

Acute Otitis Media in Children

Studies on Epidemiology, Diagnosis
and Treatment

by Leif Ingvarsson



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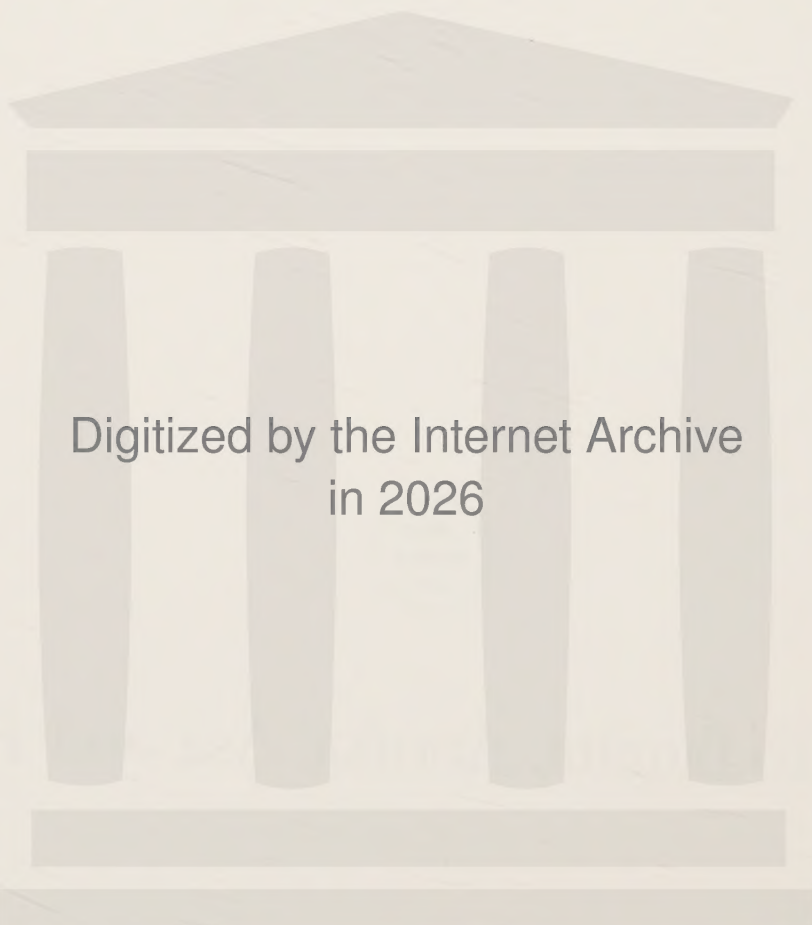
by
Leif Ingvarsson

From the Department of Otolaryngology
University of Lund
Malmö General Hospital, Malmö, Sweden

Malmö 1982



To Birgitta, Annika, Åsa and Per



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The present thesis is based on the following papers which will be referred to in the text by Roman numerals;

- I. Ingvarsson, L., Lundgren, K. & Olofsson, B.
Epidemiology of acute otitis media in children.
A prospective study of acute otitis media in children.
1. Design, Method and Material
Acta Otolaryngol (Stockh), Suppl. 388, 1982.
- II. Ingvarsson, L., Lundgren, K., Olofsson, B. & Wall, S.
Epidemiology of acute otitis media in children.
A prospective study of acute otitis media in children.
2. Incidence in an urban population.
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- III. Ingvarsson, L.
Acute otalgia in children - Findings and diagnosis.
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exudate during treatment of acute otitis media.
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- V. Ingvarsson, L. & Lundgren, K.
Penicillin treatment of acute otitis media in children.
A study of the duration of treatment.
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CONTENTS	page
DEFINITIONS	7
INTRODUCTION	9
PURPOSES OF THE INVESTIGATION	10
REVIEW OF THE LITERATURE	11
Epidemiology	
Diagnosis	
Treatment	
RESULTS	
I. A prospective study of acute otitis media in children.	15
1. Design, method and material.	
II. A prospective study of acute otitis media in children.	19
2. Incidence in an urban population.	
III. Acute otalgia in children - Findings and Diagnosis	23
IV. Concentration of penicillin V in serum and middle ear exudate during treatment of acute otitis media.	25
V. Penicillin treatment of acute otitis media in children. A study of the duration of treatment.	29
GENERAL DISCUSSION	31
SUMMARY	39
REFERENCES	41
ACKNOWLEDGEMENTS	47
PAPER I	49
PAPER II	
PAPER III	
PAPER IV	
PAPER V	

DEFINITIONS

Acute otitis media (AOM): reddened, bulging eardrum with pneumotoscopic signs of middle ear effusion or spontaneous perforation and otorrhea.

Otitis media without effusion (simplex otitis): reddened eardrum in neutral position without pneumotoscopic signs of middle ear effusion.

Serous otitis media (SOM): greyish or lightly vascular eardrum, retracted or in neutral position with pneumotoscopic signs of middle ear effusion.

Relapse: a new attack of AOM after completed antibiotic therapy and within a month after the first episode.

Therapeutic failure: insufficient effect of therapy or a new attack of AOM during antibiotic therapy.

Cohort: a well defined group of people with some given characteristic(s) in common.

Population at risk: number of children exposed to the risk of getting AOM.

Attack Rate: number of episodes of AOM (rate) per 100 children at risk per year.

Incidence Rate of the first episode of AOM =
$$\frac{\text{number of children getting their first episode of AOM}}{\text{Population at risk}} \text{ per time unit}$$

Cumulative Incidence Rate (CIR) =
$$\frac{\text{number of children getting AOM during a specified period of time}}{\text{number of children in the population at the beginning of the period}}$$

CIR is expressed in percentage.

INTRODUCTION

Acute Otitis Media (AOM) is one of the most common bacterial complications of upper respiratory tract infections in childhood causing a lot of medical, social and economic problems. AOM is still as common as in the preantibiotic era. AOM and its sequelae in Sweden are estimated to be the cause of about one million visits a year to medical doctors (Medicinska Forskningsrådet, 1978).

In view of the wide distribution of AOM, primarily among preschool children, the epidemiology of the disease is still to a large extent inadequately explored and has not received the same attention as etiologic, bacteriologic or therapeutic questions, for instance.

Children with diseases of the ENT-region are seen by different categories of doctors, mainly general practitioners, pediatricians and otologists. Diseases of the middle ear and tympanic membrane are sometimes difficult to diagnose, especially in infants and small children. The possibility of a correct evaluation of the tympanic membrane depends on the experience and otoscopic skill of the individual doctor and of the equipment available.

The introduction of antibiotics, first sulfonamides and later penicillin G in the 'forties drastically reduced the frequency of life-threatening complications. Oral penicillin V was introduced in the early 'fifties and soon became the drug of first choice in Sweden as well as in many other countries in the treatment of AOM in children. During the 'sixties and 'seventies, the size of the daily and single dose of penicillin has been increased and the administration procedure has been simplified. The usual duration of antibiotic therapy is 10 days but it has not been tested whether it need be so long (Bluestone & Shurin, 1974).

PURPOSES OF THE INVESTIGATION

The purposes of the present investigation were as follows:

1. To study the incidence of AOM in children in relation to demographic and social factors in a prospective longitudinal epidemiologic investigation.
2. To study anamnestic and symptomatic factors concerning AOM in children in order to facilitate a correct diagnosis of AOM.
3. To study the concentration of penicillin V in serum and middle ear exudate during the course of treatment of AOM and to evaluate the adequate duration of penicillin treatment.

REVIEW OF THE LITERATURE

EPIDEMIOLOGY

Most studies of the epidemiology are incidence-studies of selected groups of children followed up for a varying length of time, mostly one year. Miller (1960) found that 19 % of 847 children surveyed had at least one episode of AOM before the age of 3, and 30 % of these children had more than one attack. Lowe et al. (1963) followed up 2 000 children up to 15 years of age for one year; 6 % had at least one episode of AOM. Paterson & MacLean (1970) also followed up about 2 000 children up to 15 years of age for one year. 11 % had one episode of AOM and 19 % of these had more than one attack. Brownlee et al. (1969) examined retrospectively the medical records of 772 children followed up from birth to 5 years of age or more. 84 % of the children had had at least one episode of AOM.

AOM occurs primarily in children under 10 years of age (Nielsen, 1945; Medical Research Council, 1957; Lowe et al., 1963; Feingold et al., 1966; Brownlee et al., 1969). Different investigators have reported different peaks of the incidence of the AOM. Feingold et al. (1966) and Brownlee et al. (1969) found the highest incidence at 1-2 years of age. MRC (1957) registered a peak at 6 years. Lowe et al. (1963) found two peaks, the highest before the age of one and a smaller peak at the age of 5-6. Paavolainen (1967) and Fry (1969) found the highest incidence at 3 and 4 years of age, respectively. Most authors registered a substantial decrease in the incidence after the age of 6.

In a retrospective study Howie et al. (1975) analysed the records of 488 children from birth up to 5 years of age. Children who had had exudative otitis media before the age of 18 months had repeated recurrences in the following years. They were thus more prone to get otitis media than those who had their first episode after the age of 18 months.

In many investigations the incidence of AOM in relation to sex and season of the year were studied. Nielsen (1945), Feingold et al. (1966), Reed et al. (1967) and Eldridge et al. (1970) found a higher incidence in boys than in girls. MRC (1957) and

Lowe et al. (1963) on the other hand, did not find any differences with sex. Several investigators reported a seasonal variation in children (MRC, 1957; Fry, 1961; Lowe et al., 1963; Brownlee et al., 1969). Most episodes occurred in the winter season (November - April) and the lowest figures were registered during the summer.

Several investigations have been carried out in Eskimo- and Indian children living in Alaska and Canada since middle ear diseases are very common in children belonging to these races. This high frequency has been ascribed to genetic factors such as the shape of the skull and Eustachian tube (McEldowney & Kessner, 1972). The need of further genetic studies of high risk populations has been stressed (Eldridge et al., 1970). Also poor socio-economic conditions have been considered an important factor (Cambon et al., 1965; Ling et al., 1969; Kaplan et al., 1973). Shurin et al. (1979) and Teele et al. (1980) found higher incidences of AOM in white children than in black children.

Several authors have pointed out that the occurrence of AOM is related to poor socio-economic standard (Cambon et al., 1965; Robinson et al., 1967; Ling et al. 1969; Paterson & MacLean, 1970; Hinchliffe, 1972; Kaplan et al., 1973). Most of these studies have been performed on more or less selected groups of children.

Recent studies in Scandinavia have shown that children, cared for in larger groups, such as in day-care centers, have more episodes of AOM and upper respiratory tract infections than those cared for at home (Strangert, 1976; Vinther et al., 1979; Ståhlberg, 1980). Vinther et al. (1981) also showed higher incidences of AOM in children living in concrete buildings than among those living in brick buildings.

In a review of earlier epidemiologic studies on AOM in children McEldowney & Kessner (1972) pointed out that most previous studies were not correctly designed. With few exceptions the reports concerned with the epidemiology of middle ear disease in children do not give specific and useful information (Klein, 1978). Prospective longitudinal studies of a cohort of children from a geographically defined population are required (McEldowney & Kessner, 1972; Kudrjavcev & Schoenberg, 1979).

DIAGNOSIS

The diagnosis of AOM is often very difficult especially in infants and small children (Bluestone & Shurin, 1974; Rowe, 1975; Mortimer, 1976; Giebink & Quie, 1978; Paradise, 1980). The main symptoms, besides symptoms of upper respiratory tract infections, are ear-ache, fever, occasionally otorrhea and general irritability. However, the clinical symptoms of AOM vary and may sometimes be unspecific and directly misleading. Thus, several authors have pointed out that a firm diagnosis of AOM requires visible inspection of the eardrums (Stickler & McBean, 1964; Rubenstein et al., 1965; Sheehy, 1972; Bluestone & Shurin, 1974; Mortimer, 1976; Giebink & Quie, 1978; Paradise, 1980). An otoscopic diagnosis of AOM can be confirmed by demonstration of pathogenic bacteria in middle ear exudate (Mortimer & Watterson, 1956; Coffey et al., 1966; Halsted et al., 1968; Howie et al., 1970; Bluestone & Shurin, 1974). This, however, requires myringotomy, which is not performed routinely in out-patients in Sweden nowadays. Tympanometry is often helpful in confirming middle ear effusion (Renvall, 1975) but cannot be relied upon in the diagnosis of AOM (Paradise, 1980). Physicians lacking experience and otoscopic training thus run a great risk of over- as well as under-diagnosing AOM (Mortimer, 1976). Possibilities to facilitate the diagnosis of AOM in cases where the tympanic membrane is difficult to examine and evaluate must thus be desirable.

TREATMENT

In the preantibiotic era AOM was usually treated with surgical drainage with myringotomy and, in complicated cases, mastoidectomy. The use of antibiotics, primarily sulfonamides and later penicillin, in the 'forties and 'fifties dramatically changed the outcome of acute middle ear infections (Hamberger, 1942, Rudberg, 1954). The serious and feared complications, such as mastoiditis, labyrinthitis, meningitis and cerebral abscess, soon became rare (Ojala & Siirala, 1953). Myringotomy and antibiotics were generally accepted as the main form of therapy in the treatment of AOM. In the 'fifties, 'sixties and 'seventies a large number of other antibiotics became available, for instance, erythromycin, tetracycline, ampicillin, amoxicillin, cephalosporin and combina-

tions, such as trimethoprim-sulfamethoxazole. Numerous investigations comparing the clinical effect of different antibiotics or groups of antibiotics on AOM have been published (Stickler & McBean, 1964; Rubenstein et al., 1965; Bass et al., 1967; Howie & Ploussard, 1969; Nilsson et al., 1969; Howie & Ploussard, 1972; Howard et al., 1976). Different kinds of antibiotics or combinations of antibiotics seem to have their advocates, but penicillin V and ampicillin seem to be the two most widely used preparations nowadays. Ever since the beginning of the 'fifties the oral potassium salt of penicillin (penicillin V) has been the drug of first choice in the treatment of AOM in Sweden, as in many other countries. The penicillin V has kept its position as the drug of first choice in the treatment of AOM in children mainly because of the bactericidal effect, a minimum development of resistance, the narrowness of the bacterial spectrum, the relatively mild and unusual low frequency of adverse effects of the drug and finally its price.

Very low daily doses were used during the 'fifties and the beginning of the 'sixties leading to a large number of therapeutic failures mainly due to *H. influenzae*. Before 1966 daily doses of 13-26 mg/kg bodyweight were the rule. However, Kamme et al. (1969) showed that a single penicillin dose of 26 mg/kg bodyweight gave middle ear exudate concentrations high enough to inhibit about 90 % of all bacterial strains. As a result of these studies, the daily dose was increased to 52 mg/kg bodyweight (Lundgren, 1972).

The dosage has been simplified in Sweden. Since the early 'seventies it has been found sufficient to give a single dose of 25 mg/kg bodyweight twice a day in the treatment of AOM, acute tonsillitis and sinusitis (Edlund et al., 1974; Rundcrantz & Sundför, 1974; Ekedahl et al., 1980).

A 10-day course of penicillin V in uncomplicated cases of AOM has been used in Sweden since the 'fifties. A corresponding period of treatment has been recommended also for other drugs (Coffey et al., 1966; Bass et al., 1967; Hemenway & Smith, 1970; Lundgren, 1972; Bluestone & Shurin, 1974). The duration of treatment is based mainly on empirical experiences and no systematical efforts have been published to assess the effect of variation of the duration of penicillin therapy on the results of AOM.

I. A PROSPECTIVE STUDY OF ACUTE OTITIS MEDIA IN CHILDREN

1. DESIGN, METHOD AND MATERIAL

Epidemiologic studies of AOM have been carried out, but mostly in a selected group of children, e.g. within a limited area, in children visiting a private ENT- or Pediatric practice or in children belonging to different social or ethnic groups. In many of these studies the materials are primarily selected and vary in design, in the diagnostic methods used, and in definition of the populations studied. Prospective long-term studies of populations in a well defined geographic area are lacking (McEldowney & Kessner, 1972; Kudrjavcev & Schoenberg, 1979).

The city of Malmö is a well restricted geographic unit. The population is sufficiently large, well defined, and served by only one hospital. In addition, the official data on its population with various statistics is computerized.

In 1977 a prospective long-term epidemiologic study of AOM in children was started in Malmö. The study will continue for about 10 years.

The aims of the present investigation were: (1) to describe the organization and performance of the investigation, and (2) to present actual results of the epidemiologic study regarding the occurrence of AOM in different ages and the occurrence in relation to sex, season of the year, type of dwelling in the city and type of day-care of the children.

METHOD AND MATERIAL

All cases of AOM in children living in Malmö, otoscopically diagnosed by a doctor, were registered. All doctors in the city working in acute pediatric medical attendance participated. The registration includes the name, individual 10-digit birth number and date and place of diagnosis as well as official data on the patients' dwelling and type of day-care within the part of the city where the patient is living. The last-mentioned data are extracted from the population register of the county administration and from the official day-care register at the social welfare office. The material was then transferred to and arranged and statistically treated in a computer with a specially designed programme.

The organization of the collection of the data is illustrated in Fig. 1. In the first year of registration, 1977, all children up to 3 years of age were registered. In each of the following 2 years a new age class was included. Since 1980 children up to 15 years of age have been registered. The present report includes all cases of AOM registered from February 1st, 1977, to the end of 1980.

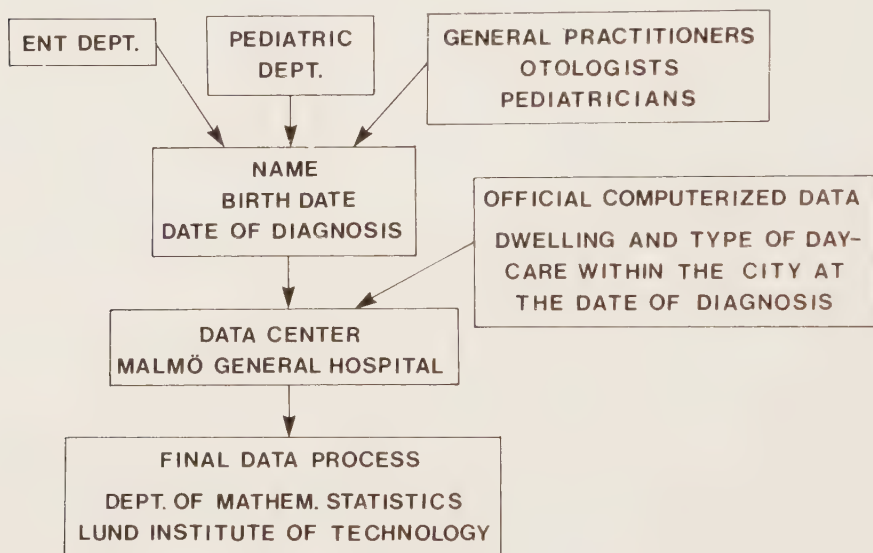


Fig. 1. Epidemiology of Acute Otitis Media in children living in Malmö. Organization of data collection.

RESULTS

During the 4 years of registration 6 932 children got totally 11 930 episodes of AOM. 2 327 (34 %) had more than one episode. Every year the disease was most common among one-year-olds, 29 % had at least one episode in 1980. Between 52 % and 55 % of all the children with AOM were boys. About 60 % of all episodes registered were diagnosed at the ENT-department, 25 % at the Pediatric department, and 14 % in other diagnostic units. AOM was most common during the winter season.

The occurrence of AOM was most common among children living in the modern villa suburb of Oxie, and these children also had the highest attack rates. The children living in the centre of the city had the lowest occurrence as well as attack rate and children in a modern apartment-house district occupied an intermediate position. 13-18 % of all children in Malmö attended day-care centers, 10-13 % attended family day-care homes and 70-76 % were cared for at home or by private child-minders during the 4 years of registration. Corresponding figures for children with AOM were 23-31 % at day-care centers, 16-17 % in family day-care homes, and 52-60 % cared for at home or by private child-minders. Most episodes of AOM per 100 children at risk also occurred in children attending day-care centers. The smallest number of AOM occurred in children cared for at home or in other private care, while children in family day-care homes occupied an intermediate position.

CONCLUSION

The present prospective long-term study of AOM in children was possible thanks to the unique conditions existing in Malmö, to the uniform design of the project and to the computer technique. The occurrence of AOM was highest among one-year-old children and did not vary significantly with sex. Seasonal variations, differences in the occurrence of AOM among children living in different districts and differences according to type of day-care were found.

II. A PROSPECTIVE STUDY OF ACUTE OTITIS MEDIA IN CHILDREN

2. INCIDENCE IN AN URBAN POPULATION

Very few cohort studies are available of the relation between AOM and demographic and socio-economic factors in an unselected population. Also studies of the incidence of AOM in children with an observation period exceeding one year are very few. Prospective long-term investigations in a sufficiently large cohort of unselected children from a well defined population have been recommended (Kudrjavcev & Schoenberg, 1979). Since 1977 a prospective epidemiologic study has been in progress in Malmö, Sweden (I).

The aims of the present investigation were: (1) to carry out a descriptive study of the incidence of AOM in birth cohorts of children born in 1977-1980, and (2) to analyse the possible influence of different demographic and social factors on the observed incidence of AOM.

MATERIAL

Since 1977 all cases of AOM in children living in Malmö, otoscopically diagnosed by a doctor, have been registered (I). Every separate birth cohort of children born in 1977 to 1980 were extracted from the total material. The 4 birth cohorts, each including about 2 200 children, were followed up till the end of December 1980 implying a maximum of 48 months of observation.

The age-specific incidence rates and the cumulative incidence rate (CIR) of the first episode of AOM were studied with the method of the life-table.

The 4 cohorts of children living in Malmö were corrected according to in- and out-moving during the 4 years of observation. The birth cohort of children born in 1977 had the longest observation time (48 months) and the principal part of the results refers to this cohort.

RESULTS

In the children born in 1977 in Malmö, 1 101 (about 54 %) children had at least one episode of AOM during the 4 years of observation

and 48 % of them had more than one episode.

The highest age-specific incidence rate (per 1000 months⁻¹ follow-up) was found in the age interval 6-11 months. The CIR, calculated from the age-specific incidence rate, (Fig. 2) showed that 56 % of the boys and 53 % of the girls had had at least one episode of AOM by the end of the observation period (48 months). In the children, who got their first episode of AOM before the age of 18 months, 19 % had 4 or more episodes. The corresponding figure for the children who had their first episode after the age of 18 months was 3 %. The differences between the two groups were significant. A typical seasonal variation was seen with the largest number of episodes from October to April with a peak in December and the lowest number of diagnoses registered in July and August.

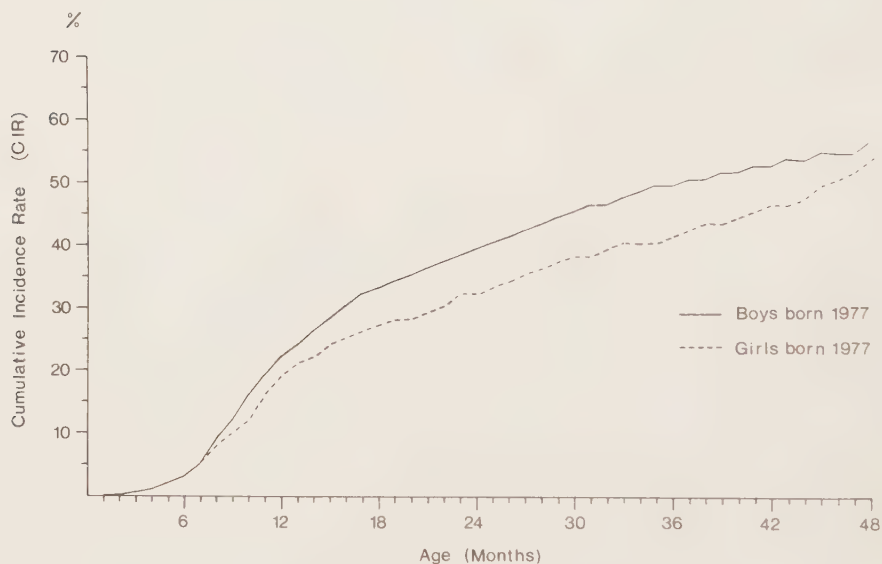


Fig. 2. Cumulative incidence rate (CIR) of the first episode of AOM in relation to sex.

The highest age-specific incidence rates for children living in three districts with different types of housing were seen in the age interval 6-11 months and were 41.5, 33.8 and 20.3 in Oxie, Rosengård and the centre of the city, respectively.

The CIR of AOM in children for the three districts differed significantly. At the end of the observation period (48 months) about 65 % of the children living in modern villas in Oxie, 49 % of the children in the modern but crowded apartment-house district in Rosengård and 40 % of the children living in mixed, mostly modern apartment-houses, in the centre of the city had had at least one episode of AOM.

The distribution between different types of day-care differed significantly in relation to the number of episodes of AOM. Children attending day-care centers were more prone to have recurrent episodes than home-cared children.

There were no differences in the distribution of children among different types of day-care in the different districts of the city.

CONCLUSION

The cohort study showed that children in the age interval 6-11 months run the greatest risk of getting AOM within their first 4 years of life. There was no difference with sex, but the boys had significantly higher CIR than the girls. Children who had their first episode before the age of 18 months were significantly more prone to have recurrences than those who had their first episode after the age of 18 months. Significant differences in the incidence rate were found between districts with different types of housing. Children attending day-care centers run a greater risk of having recurrent episodes of AOM than those cared for in family day-care homes, at home or by private child-minders.

III. ACUTE OTALGIA IN CHILDREN - FINDINGS AND DIAGNOSIS

Symptoms of AOM in children are generally ear-ache (otalgia), fever and occasionally otorrhea combined with upper respiratory tract infection (URI). However, the clinical symptoms of AOM vary and are sometimes unspecific or directly misleading, for which reason a firm diagnosis requires visual inspection of the eardrums. The otoscopic examination may be difficult and the risk of an incorrect diagnosis varies inversely with the experience and otoscopic skill of the examiner. In cases where the eardrums are difficult to examine, the diagnosis of AOM is therefore often based only on symptoms of otalgia, fever and/or URI or other symptoms.

The aim of this investigation was to find out whether otalgia or any other symptom is so closely associated with AOM as to make otoscopic examination unnecessary in the diagnosis of the condition.

MATERIAL

The material consisted of 171 children up to 15 years of age and seen at the ENT-department, General Hospital, Malmö, because of otalgia and suspected AOM. Otalgia was reported by the patients and/or by the parents. Examination included inquiry about the duration of otalgia, fever, any co-existing URI and signs of otorrhea. All children were otomicroscopically examined and the diagnosis was based on this examination. The following classification was made:

1. Acute (purulent) Otitis Media (AOM)
2. Otitis Media without effusion (simplex otitis)
3. Serous Otitis Media (SOM)
4. Normal eardrums

Seventy-three children with AOM were treated with penicillin V and 6 children with erythromycin. In 25 cases of simplex otitis and in 30 cases of SOM, the children were treated with a decongestant but no antibiotics. All children with AOM were re-examined immediately after the end of treatment. Children with simplex otitis were re-examined for the first time after 2-3 days. All children were followed up for at least 3 months.

RESULTS

AOM was diagnosed in 79 (46 %), simplex otitis in 25 (15 %) and SOM in 30 (17 %) of the children. Normal eardrums were found in 37 (22 %) cases. Examination of the relation between symptoms and otomicroscopic diagnosis showed that 78 % of the children had had otalgia for less than 24 hours, symptoms on URI were described by 82 %, fever was noted in 53 % of the children. Children with AOM differed significantly from the other children in this respect. 78 % had fever compared with 30 % of the other children. Otorrhea was noted in 24 (30 %) of the children with AOM and was found in nearly half of the children (44 %) under 2 years of age. In most of the children who had not AOM (54 %), the otalgia could be classified as referred pain due to, for instance, discomfort when swallowing, nasal obstruction or throat pain. Other reasons were general irritability due to fever, teething or moderate hearing loss.

CONCLUSION

The study showed that AOM was diagnosed in less than half (46 %) of the children with otalgia. Symptoms such as otalgia, otorrhea, fever or URI, possibly except for the combination of otorrhea and fever, can occur without AOM. A correct otoscopic examination and evaluation of the eardrums is therefore necessary in children with otalgia, other symptoms of URI and in doubtful cases of acute illness. A single symptom or a combination of symptoms cannot replace adequate, otoscopic examination in the diagnosis of AOM.

IV. CONCENTRATION OF PENICILLIN V IN SERUM AND MIDDLE EAR EXUDATE DURING TREATMENT OF ACUTE OTITIS MEDIA

The therapeutic effect of antibiotics depends on the concentration of the drug at the site of infection. Serum levels after therapeutic doses of all antibiotics are known, but the corresponding concentrations at the site of infection have not been studied to the same extent. Acute purulent otitis media is suitable for such assessment. The concentration of penicillin V in serum and middle ear exudate in children with AOM was determined after the first dose of a 10-day course of treatment (Kamme et al., 1969). No corresponding determinations of the penicillin concentration during the course of treatment have been performed.

The aim of the present investigation was: to determine the concentration of penicillin V in serum and middle ear exudate and to isolate bacteria in the ear exudate during the course of treatment with penicillin V in AOM in children.

MATERIAL

Sixty-one patients, aged 6 months to 10 years, admitted to the ENT-department, Malmö General Hospital, with acute purulent otitis media (AOM) were treated with penicillin V for 10 days. The drug was given twice a day in a total dose of 50 mg/kg bodyweight. The concentration of penicillin was determined in serum and in middle ear exudate on one of the first six days of treatment; 60, 120 or 180 minutes after administration of the drug. Material for bacterial culture was taken from the nasopharynx before and during treatment and from the middle ear exudate at the time of myringotomy. The samples were collected simultaneously under general anaesthesia.

RESULTS

Figure 3 gives the range and mean values of serum and middle ear exudate concentrations of penicillin V 60 minutes after administration of the drug during the first 6 days of treatment. The mean serum concentration of penicillin V decreased during treatment, but the decrease was not significant. There was a significant decrease in penicillin concentration in the middle ear exudate

during treatment. This decrease was most pronounced during the first two days when the concentration fell to a significantly lower level. In a few cases, *H. influenzae* were found in the middle ear exudate at the time of myringotomy. In these cases the concentration of penicillin in the exudate was found to be higher than the mean concentration at corresponding times.

The areas under the mean serum and mean exudate concentration curves (area under the curve = AUC) were larger after the first 2 doses than after the 8th and 12th doses. The 0 to 180-minute-exudates AUC after the 8th and 12th doses were 44 % of that in the first stage of therapy and the difference was statistically significant ($p = 0.002$).

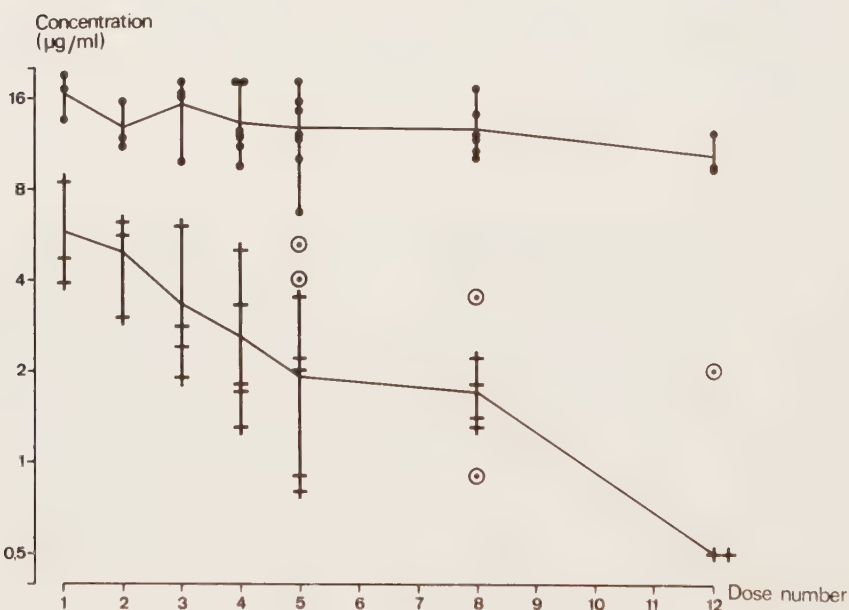


Fig. 3. Concentration (range and mean) of penicillin V in serum(●) and middle ear exudate (+) during the first six days of treatment. Determinations performed 60 minutes after administration of a mean dose of 25 mg/kg bodyweight (33 patients). ○ - Growth of *H. influenzae* in middle ear exudate.

CONCLUSION

The initially high exudate penicillin concentration in children with AOM decreased rapidly to a significantly lower level 2 to 3 days after the beginning of the therapy and remained so during the rest of the treatment period. The investigation produced no strong evidence for the need of a 10-day course of treatment.

V. PENICILLIN TREATMENT OF ACUTE OTITIS MEDIA IN CHILDREN

A STUDY OF THE DURATION OF TREATMENT

Studies of the exudate concentration of penicillin V in AOM in children (IV) showed that the initially high exudate concentration decreased to a significantly lower level already after 2-3 days of treatment and persisted during the rest of the treatment period indicating the cessation of the inflammatory reaction. One might therefore question whether the penicillin-treatment of 10 days in AOM can be shortened without impairing the results of healing or without increasing the risk of complications.

The aims of the present study were: (1) to compare the effect of treatment with penicillin V for 5 and 10 days, respectively, in children with AOM, and (2) to find out whether a further increase in the penicillin dose would have a beneficial effect.

MATERIAL

Two hundred and ninety-seven children, aged 6 months to 7 years, with AOM were treated with penicillin V. One hundred and forty-eight children were given 25 or 50 mg/kg bodyweight twice a day for 5 days and 149 children 25 mg/kg bodyweight twice a day for 10 days. Nasopharyngeal material for bacterial culture was collected at the time of diagnosis and 10-12 days after the first consultation (control 1). After 28-30 days (control 2) healing was assessed. Healing was said to have occurred when the drums had a normal otoscopic appearance and mobility and, in patients that could be examined, also normal hearing. All children were followed up at least 6 months.

RESULTS

No differences were found in the rate of healing between the 5- and 10-day-groups ($p > 0.2$) (Table I). The larger penicillin dose, which was given to half the 5-day-group, did not lead to improved healing. Among the 297 children, 66 (22 %) did not meet the criteria for healing after one month, most often (42 cases) because of persistent SOM. A relapse was noted in 18 cases and therapeutic failure in 6. The four groups did not differ regarding persisting SOM, relapse or therapeutic failure ($p > 0.2$) New attacks of AOM

(recurrences) within 6 months after control 2 were noted in 27 % (22-30%) of all children. In all the four groups recurrences were more common among the children below 2 years of age than in the older ones and no difference in frequency of recurrences was found between 5- and 10-day-groups.

Table I. *Healing rate in relation to dose and duration of treatment judged at control 2.*

Treatment	No. of children	<u>Healed</u>		<u>Not healed</u>		<u>Cause of absence of healing</u>		
		No.	%	No.	%	SOM	Relapse	Therapeutic failure
2Nx 5	82	64	78	18	22	10	6	2
Nx10	81	60	74	21	26	16	4	1
Nx 5	66	53	80	13	20	8	4	1
Nx10	68	54	79	14	21	8	4	2
Total	297	231	78	66	22	42	18	6

Normal dose (N): 25 mg/kg bodyweight twice a day

CONCLUSION

The investigation showed that treatment of AOM with penicillin for 10 days can be reduced to 5 days with maintained satisfactory healing and without the risk of increasing complications such as SOM, relapses or therapeutic failure. Nor does the risk of a recurrence of otitis increase.

GENERAL DISCUSSION

Acute Otitis Media and its sequelae in children still give rise to great medical, social and economical problems although the difficult and life-threatening complications dreaded in the preantibiotic era have now virtually disappeared. Our statistical records at the ENT-department, Malmö General Hospital, show no evidence of the disease having decreased in frequency. On the contrary, during the last two decades it has, if anything, increased at least in urban populations.

Problems concerning the epidemiology, diagnosis and treatment of AOM are intimately inter-related. A correct diagnosis of AOM is, of course, of great importance in the epidemiologic investigation of the condition and in its treatment.

An epidemiologic survey of the incidence of AOM in a population must be based on the otoscopic diagnosis of the condition by the participating doctors. The reliability of a survey thus depends on the experience and otoscopic skill of the individual examiner. If the participating doctors are few and well trained, such as otologists with adequate technical equipment, the degree of reliability will probably be high. On the other hand, if a whole population is to be surveyed, all doctors, even non-specialists, working within the area have to participate. The study then naturally includes the risk of interindividual differences in the diagnostic skill and experience of the doctors and the validity of the results may be impaired by over-diagnosis as well as by under-diagnosis. This source of error is encountered in practically all epidemiologic studies of clinical conditions though not in survival studies, for example.

The diagnosis of AOM is equally important in the discussion of the treatment of the condition. According to current principles in Sweden, as in many other countries, purulent acute otitis media, as a rule, should be treated with antibiotics, but not simplex otitis or serous otitis media. If in a given case a doctor is uncertain whether the condition should be classified as purulent AOM or a milder disorder not requiring antibiotic treatment, he may prescribe such treatment for safety's sake. Such uncertainty due to lack of diagnostic skill must unavoidably often lead to over-diagnosis and over-treatment.

EPIDEMIOLOGY

The incidence of AOM in children is difficult to assess. That the disease is one of the most common bacterial complications of upper respiratory tract infection is all too well known to every general practitioner, pediatrician and otologist. However, the many investigations performed through the years have produced more or less reliable figures for the incidence of the condition. The difficulties in covering a whole population and in making a correct diagnosis of "acute middle ear disease" are some of the factors capable of impairing the reliability of an incidence study. Most earlier studies of the incidence of AOM in epidemiological investigations have therefore been performed in small insolated communities, such as in Eskimo- or Indian villages or other native populations (Cambon et al., 1965; Reed et al., 1967; Ling et al., 1969; Eldridge et al., 1970; Kaplan et al., 1973). Studies performed in urban populations, in Europe for instance (Nielsen, 1945; Lowe et al., 1963; Paavolainen, 1967; Paterson & MacLean, 1970; Vinther et al., 1979) or the U.S.A. (Brownlee et al., 1969; Teele et al., 1980) are mostly selected in one way or another, e.g. children in a restricted area, children belonging to a certain social group and children visiting a specific pediatric or otolaryngologic practice. Most studies are retrospective and are often based on evaluation of medical records.

Many of the above mentioned factors constituted the background of an epidemiological, prospective, long-term study of the incidence of AOM in children in Malmö. The possibilities of realizing such a study are unique in the city of Malmö. The city is a modern industrial and commercial center in southern Sweden with a well defined area, served by a single hospital. The official data on its population with various statistics are computerized. Housing standards and dwelling conditions are well documented. The individual 10-digit birth number of every inhabitant in Sweden means that any individual can be readily identified and that information about the dwelling of any child within the city and about the main type of day-care can be obtained from official computerized population registers.

About 75 % of all pediatric medical service in the city is given at the only hospital, Malmö General Hospital; the rest, by

a relatively small number of general practitioners in public service and private practising otologists and pediatricians. Emergencies in the evenings, nights and week-ends are taken care of by the ENT- and Pediatric departments at the hospital and by two emergency services outside the hospital.

Members of the above-mentioned departments and doctors readily accepted to participate in the investigation. Thanks to their cooperation the material included the greatest possible number of episodes of AOM in the actual age groups.

Of the birth cohort born in 1977, 54 % had at least one episode of AOM before the age of 48 months and 48 % of these children had had more than one episode. These figures are very high, at least compared with those in some other studies (Miller et al., 1960; Lancet, 1970). More than 80 % of the cases of AOM occurred in preschool children. Similar distributions have been reported by other investigators (MRC, 1957; Lowe et al., 1963; Paavolainen, 1967).

In the study (I) more boys than girls were found to have AOM. However, this difference was not significant because there were more boys than girls in the population. These circumstances may probably explain the sex differences found in some of the earlier investigations, where no corrections were made for differences in the sex distribution of the total population. However, the present incidence study of the birth cohorts of children born in 1977-1980 (II) revealed a significantly higher cumulative incidence rate (CIR) in the boys than in the girls roughly between 12 and 42 months of age.

The CIR showed that the risk of getting AOM before the age of 6 months was negligible. However, in the following age interval (6-11 months) the children run the greatest risk of getting AOM within the first 4 years of life. This can probably be explained by the disappearance of the maternal immunoglobulins and an immature immune defence system as well as increased exposure to upper respiratory tract infection.

The children who had their first episode of AOM before the age of 18 months were significantly more prone to have recurrences than those who had their first episode after the age of 18 months. Corresponding results have been reported by Howie et al. (1975).

It is important to identify the otitis-prone children early in life. This requires more knowledge of the epidemiology of the condition.

The children living in a modern villa suburb (Oxie) had a higher attack rate and age-specific incidence rate than those in other districts, such as Rosengård with its crowded area of modern concrete apartment-houses and the centre of the city with its mixed, mostly modern or modernized, brick apartment-houses. Since AOM is a complication of URI, it is plausible to assume that the number of URI is larger among the children living in Oxie than among those in the other districts of the city. At present any explanation cannot be offered for the higher figures found for Oxie, but factors, such as type and quality of housing and the immediate environment, differ between the districts mentioned. There may be differences in air humidity, passive smoking and ventilation in the houses. The new modern villas are well insulated and in order to save heating costs they may be less well ventilated and this may influence the environmental conditions for the children.

It was also found that children dwelling in day-care centers were more prone to get AOM and recurrences than children cared for at home or in family day-care homes. Similar findings have been made by other investigators (Strangert, 1976; Vinther et al., 1979; Ståhlberg, 1980). This proneness was assumedly due to the greater possibilities of transmission of URI in the larger group of children in the day-care centers.

It would be reasonable to suspect that the children who were living in Oxie and who had the highest incidence of AOM were also cared for in day-care centers more often than children living in the other districts. However, no such connection could be demonstrated.

The study is to go on for about 10 years and a "case-control" study is planned in order to obtain more detailed information of the relation between the incidence of AOM in children and demographic and socio-economic factors.

DIAGNOSIS

The investigation showed that the symptoms of otalgia or other symptoms of acute URI, including fever, were not specific, except perhaps for combined otorrhea and fever which virtually meant AOM. AOM was diagnosed in less than half (46 %) of the children examined. The rest of the children should thus not be routinely treated with antibiotics. Thus, otalgia alone is not enough to assume AOM; diagnosis of the condition therefore requires otoscopic examination. The uncertainty must be still greater in cases where the symptoms provide no clue whatsoever. It is therefore understandable if doctors with little or no experience of otoscopy are often unable to judge the eardrums and therefore prescribe treatment solely on the basis of the symptoms.

For practical reasons it is not possible for all cases of acute illness in children with suspected middle ear disease to be examined by an otologist, especially not in rural districts, small villages and towns where no otologist is available. In Sweden, general practitioners and pediatricians are not obliged to have received any training in otologic examination methods. This situation is very unsatisfactory concerning the demands in quality and safety of pediatric otolaryngology.

TREATMENT

Myringotomy and antibiotic treatment have been generally accepted as treatment of AOM in children. During the 'sixties and 'seventies studies were published comparing myringotomy and antibiotic treatment versus antibiotic treatment alone (Roddey et al., 1966; Lorentzen & Haugsten, 1977). These studies showed no difference in healing rates between the two methods. However, other investigators have shown that supplementary myringotomy improves healing (Qvarnberg & Palva, 1980; Qvarnberg, 1981). The value of myringotomy lies beyond the scope of the present investigation and will not be discussed here.

In Sweden, AOM is nowadays usually treated with antibiotics alone. The usually recommended antibiotic for AOM in children is penicillin V in an oral dose of 25 mg/kg bodyweight, twice a day for 10 days. This dose has been found to be high enough to inhibit most of the strains, even *H. influenzae*

(Kamme, 1969) responsible for the acute purulent middle ear infection. This dose is based on earlier studies of the penicillin concentration in middle ear exudate concentration (Kamme et al., 1969) in the acute stage of the infection. In a study of a non-inflammatory condition ("catarrhal otitis"), Lahikainen (1970) found very moderate concentrations in middle ear exudate compared with those in the acute stage of AOM (Kamme et al., 1969). Lahikainen assumed this to be due to poorer capillary permeability of the middle ear mucosa owing to the mild inflammatory condition.

It was therefore reasonable to wonder whether the penicillin concentration decreased in association with abatement of the inflammation during the course of treatment. The important thing must be maintenance of a high concentration throughout treatment at the site of infection, e.g. in middle ear exudate.

The results of the study of middle ear exudate concentration of penicillin V revealed that the concentration decreased already after 2-3 days of treatment even though the serum concentration was unchanged (IV). Only in cases of therapeutic failure, where resistant strains of *H. influenzae* were cultured from middle ear exudate did the concentration remain at a high level indicating continuation of the inflammatory reaction.

The rapid decrease in the exudate concentration of the drug due to the abatement of the inflammation 2-3 days after the beginning of the therapy may suggest that the patient responded to the treatment. It is the initial concentration of the drug that decides whether an infection will respond to the therapy or not.

In view of these findings there was no strong evidence for the need of a 10-day course of treatment of AOM in children. A clinical trial, where 5 and 10 days of treatment with penicillin V in AOM in children were compared (V) revealed no difference in the healing rates referable to the duration of treatment with penicillin. Neither was there any evidence that treatment with penicillin for 5 days instead of 10 days meant an increased risk of complications, such as SOM, relapses or therapeutic failure. Nor did the risk of a recurrence increase.

In a pilot investigation (III) of the 73 children treated with penicillin V, two groups treated for 2 and 10 days,

respectively, were compared. There was no difference in healing rate between the two groups. The material was too small to warrant any conclusion about a 2- versus a 10-day course of treatment, but a 2-day course with penicillin V would probably be enough in most uncomplicated cases of AOM in children. However, treatment for 2 days leaves too narrow a safety margin, for which reason I considered a 5-day course to be more appropriate. Since the beginning of December 1980 about 2 000 cases of AOM have been treated with penicillin for 5 days at the ENT-department in Malmö. A follow-up of 390 cases treated in this way between December 1980 and February 1981 showed that the healing rate was as good as that in the clinical study (V). No complications other than occasional cases of SOM, therapeutic failure and relapse were noted (Ingvarsson & Lundgren, 1981).

The shortening of the treatment with penicillin V from 10 to 5 days in AOM has been readily accepted by the patients and parents, not least for practical and economical reasons. In view of the frequency of this disease in childhood, mostly in infants and small children, such a shortening of the treatment would be advantageous if it could be practised in the whole country, since it would reduce the total consumption of antibiotics in children and thereby the risk of resistance developing among existing sensitive bacterial strains and the risks of allergic reactions.

Some authors (Diamant & Diamant, 1974; Thomsen et al., 1980; Van Buchem et al., 1981) claim that antibiotic treatment could be avoided in most cases of AOM. Diamant & Diamant (1974) recommended that all patients should be myringotomised and controlled about twice a week and only patients with threatening or existing otitic complications should be treated with antibiotics. According to Thomsen et al. (1980), an attitude of "masterful inactivity" towards antibiotic treatment of AOM is justifiable.

For several reasons it is difficult to share these opinions. It cannot be medically or ethically justifiable to expose children to the risk of otitic complications dreaded in the preantibiotic area, no matter how small the risk might be. Many of the children would also experience more pain and fear and,

finally, it would not be possible to control all these patients twice a week.

A correct otoscopic examination and evaluation of the eardrums to avoid over-diagnosis, and an antibiotic therapy based on an adequate dosage and duration of treatment are in my opinion the best way to deal with AOM in children.

SUMMARY

In prospective investigations of the epidemiology, diagnosis and treatment of acute otitis media (AOM) in children living in Malmö the following observations of interest were made:

EPIDEMIOLOGY

AOM was most common in one-year-olds, about 30 % of this age class had at least one episode in one year.

Children, aged 6-11 months, run the greatest risk of getting AOM. Of the children born in 1977, 54 % had at least one episode before the age of 48 months and 48 % of these children had more than one episode.

There was no difference with sex, but the boys had higher cumulative incidence rate (CIR) than the girls.

Recurrent episodes were significantly higher in children having their first episode before the age of 18 months.

The CIR was higher among children in a modern villa suburb compared to those in a modern apartment-house district or in the centre of the city.

Children at day-care centers run a greater risk of getting recurrent AOM than those at home or in family day-care homes.

DIAGNOSIS

AOM was diagnosed in less than half (46 %) of the children with otalgia.

Symptoms such as otalgia, otorrhea, fever or upper respiratory tract infection, possibly except for the combination of otorrhea and fever, can occur without AOM. A single symptom or a combination of symptoms cannot replace adequate, otoscopic examination in the diagnosis of AOM.

TREATMENT

The initially high exudate penicillin concentration in children with AOM decreased rapidly to a significantly lower level 2 to 3 days after the beginning of the therapy and remained so during the rest of the treatment period.

Treatment of AOM with penicillin for 10 days can be reduced to 5 days with maintained satisfactory healing and without the risk of increasing complications.

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L. Ingvarsson, M.D.
 Dept. of Otolaryngology
 University of Lund
 Malmö General Hospital
 S-214 01 Malmö
 Sweden

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ACTA OTO-LARYNGOLOGICA
SUPPLEMENT 388

EPIDEMIOLOGY OF ACUTE OTITIS MEDIA IN CHILDREN

by

Leif Ingvarsson, Kaj Lundgren, Bertil Olofsson
and Stig Wall

*From the Department of Otolaryngology, University of Lund,
Malmö General Hospital, Malmö, and the Department of
Mathematical Statistics, Institute of Technology, University
of Lund, Lund, and the Department of Preventive and Social
Medicine, University of Umeå, Umeå, Sweden*

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CONTENTS

1. *L. Ingvarsson, K. Lundgren and B. Olofsson*: A prospective study of acute otitis media in children. Design, Method and Material 3
2. *L. Ingvarsson, K. Lundgren, B. Olofsson and S. Wall*: A prospective study of acute otitis media in children. Incidence in an urban population 29

A PROSPECTIVE STUDY OF ACUTE OTITIS MEDIA IN CHILDREN

1. Design, Method and Material

Leif Ingvarsson¹, Kaj Lundgren¹ and Bertil Olofsson²

From the ¹Department of Otolaryngology, University of Lund, Malmö General Hospital, Malmö, and the ²Department of Mathematical Statistics, Institute of Technology, University of Lund, Lund, Sweden

Abstract. Since 1977 diagnosed attacks of acute otitis media (AOM) in children living in Malmö, Sweden, have been registered in a prospective longitudinal epidemiologic study. The study is planned to continue for about 10 years. The registration includes date of birth and date and place of diagnosis in 6 932 children with AOM as well as official data on the patient's dwelling and type of day-care within the city. In 1977 all children up to 3 years of age were registered. In each of the following 2 years a new age class was included. Since 1980 children up to 15 years have been registered. The disease was most common among one-year-olds, 29 % had at least one episode during 1980. The occurrence did not vary with sex. AOM was most common during the winter season. Children living in a modern villa suburb had AOM more often than those living in the centre of the city. The occurrence of AOM was highest among children in day-care centers.

Acute Otitis Media (AOM) is one of the most common bacterial infections of childhood and gives rise to serious medical and socio-economic problems. The epidemiology of AOM in children is still to a great extent inadequately explored despite the wide distribution and occurrence of the disease (Hinchliffe, 1972; McEldowney & Kessner, 1972; Manning et al., 1974). Epidemiologic studies of AOM have been carried out in different parts of the world, but mostly in a selected group of children, e.g. within a limited area, in children visiting a private ENT- or Pediatric practice or in children belonging to different social or ethnic groups (Medical Research Council, 1957; Lowe et al., 1963; Cambon et al., 1965; Paavolainen, 1967; Brownlee et al., 1969; Eldridge et al., 1970; Kaplan et al., 1973; Howie et al., 1975). In many of these studies the materials are primarily selected and vary in design, in the diagnostic methods used, and in definition of the populations studied. Thus, these studies are not comparable and the results are hard to evaluate. Prospective longitudinal studies within a geographically well defined population are recommended (Kudrjavcev & Schoenberg, 1979).

At the ENT-department, Malmö General Hospital, investigations of various problems concerning middle ear diseases in children have been going on since the middle of the 'seventies. Diagnostic, bacteriologic and therapeutic aspects of AOM have been studied. Current questions concerning the occurrence, onset and provocative factors have been discussed. Malmö is a city well suited to epidemiologic studies as its area is well defined and is served by only one hospital. These circumstances have been used in earlier epidemiologic studies of different diseases, e.g. in co-operation with WHO (Sternby, 1968; Isacsson, 1972).

The current study was started in 1977 and is planned to continue for about 10 years. The purpose of this long-term study can be summarized as follows:

- to assess the occurrence of AOM in children in a defined population,
- to elucidate demographic, environmental and socio-economic factors possibly influencing the occurrence of AOM observed; and
- to study the children with recurrent episodes of AOM early in life in an effort to detect possible medical and/or environmental

factors distinguishing these patients from healthy children.

The aims of the present report are:

- to describe the organization and performance of the investigation; and
- to present actual results of the epidemiologic study regarding the occurrence of AOM in different ages and the occurrence in relation to sex, season of the year, type of dwelling in the city and type of day-care of children.

METHOD AND MATERIAL

A. Organization and performance of the study

All cases of AOM diagnosed in children living in Malmö are registered on special forms. The registration includes the name of the patient, individual ten digit birth-number and date and place of diagnosis. At the ENT-department, Malmö General Hospital the forms are delivered, information computerized and checked against the official computerized population register of the city. The information about the patients is supplemented with information on their dwellings and type of day-care within the city at the time of diagnosis. These data are extracted from the population register of the county administration and from the official day-care register at the social welfare office. The material was then transferred to, arranged and statistically treated, in a computer with a specially designed programme. The organization of the data collection is illustrated in Fig. 1. The patient's name was used only when filling in the registration form and was needed only in cases where the individual's ten digit birth-number was missing. At the continued operation only the individual birth-number was used as identification number in the data file, according to ethical regulations.

B. Registration

The study was started February 1st 1977 and is planned to continue for about 10 years. The present report includes all cases of AOM up to the end of 1980. Thus, the first year (1977) comprises only 11 months. In the first year all children up to 3 years of age were

included. This implies that in January 1978, 1979 and 1980, 4-year-old, 5-year-old and 6-15-year-old children, respectively, were not registered. The material thus included all children mentioned above living in the city of Malmö and in whom AOM (primary and relapses) were otoscopically diagnosed.

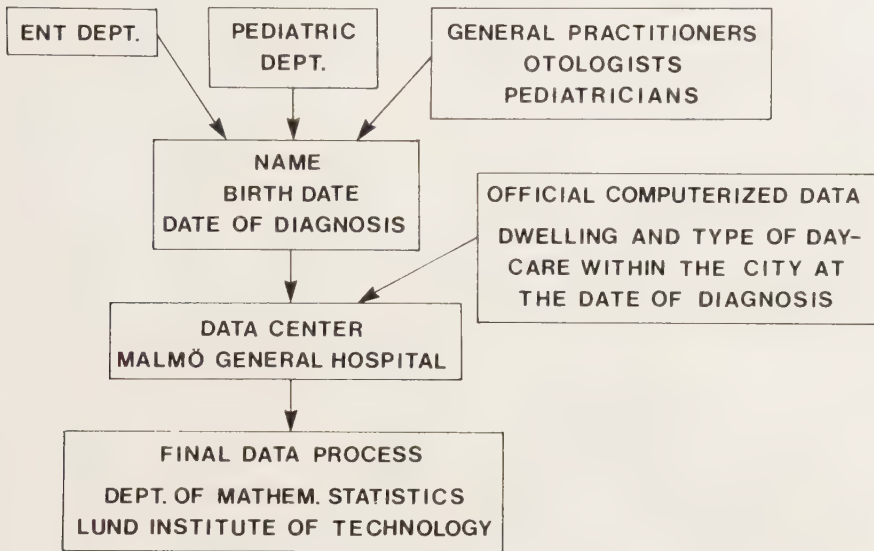


Fig. 1. Epidemiology of Acute Otitis Media in children living in Malmö. Organization of data collection.

C. Computer programme and statistical management

The material was treated by a "New Mathematical Statistics Package" (NMSP), developed at the Department of Mathematical Statistics, Institute of Technology, University of Lund, Lund, Sweden (Persson, 1981). At each registration, information about the following items were available: individual ten digit birth-number, date of diagnosis, district in the city, type of day-care, diagnostic unit and number of earlier diagnoses (since the start of the registration). During the continued management other variables were generated, e.g. sex, age at the time of the episode of AOM. Statistical analyses were done with the χ^2 -test.

D. *Organization of pediatric medical attendance*

Of all children in Malmö requiring medical help about 75 % are seen at the hospital. ENT-symptoms are diagnosed and treated at the ENT- and Pediatric departments. The remaining pediatric medical service is taken care of by about 10 general practitioners in public service and about 10 private practising otologists and pediatricians. In the evenings and nights and during week-ends emergencies are taken care of by the above-mentioned departments and by 2 ambulatory doctors on duty. In 1980, an emergency service was started outside the hospital, partly to replace the two above-mentioned doctors on duty. In the present study all diagnostic units mentioned were included. The ambulatory doctors on duty and the emergency service did not participate in the registration until the beginning of 1980.

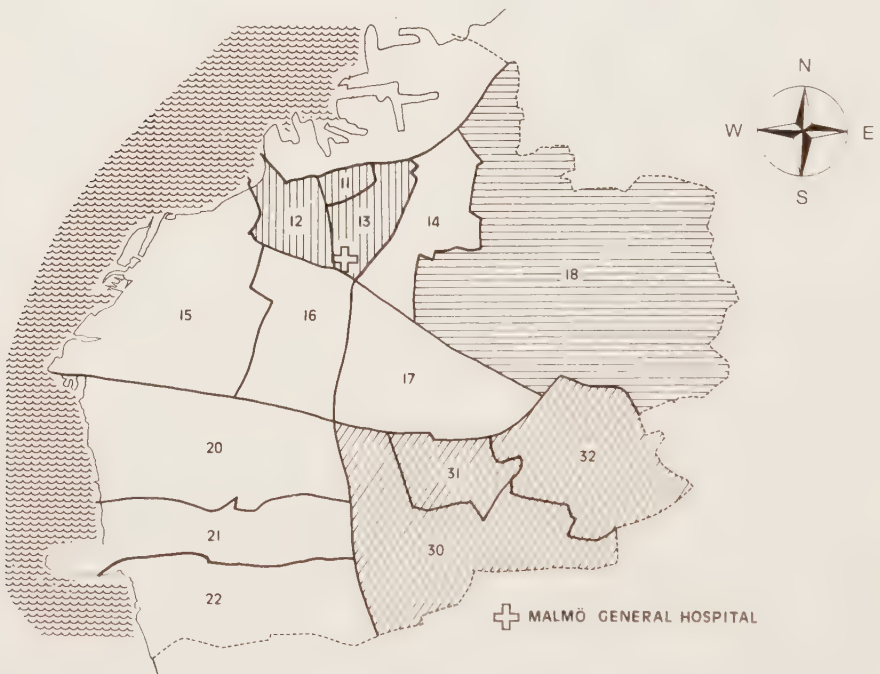


Fig. 2. Geographical division of the districts in the city of Malmö (see Table I).

Table 1. *Quarters, dwelling districts and main types of houses in the city of Malmö*

Quarter	District	Main types of houses
City	11 - 13	Apartment houses (fairly old, good standard)
Sofielund + Kirseberg	14	Apartment houses (modern + old)
Linhamn	15	Mixed, mainly villas
Hyllie	16	Modern apartment houses + villas
Fosie	17	Modern apartment houses + villas
Rosengård + Husie - Sallerup	18	Modern apartment houses + villas
Bunkeflo + Tygelsjö - V:a Klagstorp	20 - 22	Villa area (mainly modern) + rural
Oxie	30 - 32	Modern villa area + rural

Table II. *Distribution of the population among different districts in Malmö 1977 - 1980*

District	Year of registration					
	1977 (0-3 years)		1978 (0-4 years)		1979 (0-5 years)	
	No.	%	No.	%	No.	%
11-13	1380	15	1661	15	2052	15
14	705	7	848	7	982	7
15	735	8	922	8	1130	9
16	1446	15	1699	15	1991	15
17	2040	22	2389	21	2708	20
18	2069	22	2581	23	2999	22
20-22	474	5	585	5	665	5
30-32	548	6	727	6	925	7
Total	9397	100	11412	100	13452	100
					37347	100

E. Population

In 1977 Malmö had about 235 000 inhabitants, 38 500 of whom were children up to 15 years of age. Each age class covered 2 200 to 2 700 children. The city is divided into a number of statistical districts (dwelling districts) and the traditional quarters of the city consist of one or more of these districts. This geographical division is used in the following presentation of the results. Table I and Fig. 2 illustrate the different quarters of the city, the corresponding districts and the principal type of dwellings in the different districts. The distribution of the population among different districts in the years 1977-1980 is given in Table II.

Public child care: In Sweden day-care centers and family day-care homes, in which a woman cares for both her own and one to four other children, are the main forms of public out-of-home care of children up to 11 years of age. Children not looked after by the public child care service are cared for at home or by private child-minders. An example of the age distribution of the children among different types of day-care is given in Table III (March 1978). The distribution was practically the same during 1977-1980.

Table III. Age distribution of children among different types of day-care (March 1978)

Age class	Types of day-care						Total
	Public day- care centers		Family day- care homes		Home-care or other private care		
	No.	(%)	No.	(%)	No.	(%)	
< 2	183	(4)	176	(4)	4265	(92)	4624
2	463	(19)	422	(18)	1521	(63)	2406
3	559	(23)	434	(18)	1400	(58)	2393
4	610	(26)	437	(19)	1311	(55)	2358
5	575	(25)	390	(17)	1320	(58)	2285
6	583	(24)	366	(15)	1472	(61)	2421
7	517	(22)	387	(17)	1412	(61)	2316
8-11	699	(7)	943	(9)	8591	(84)	10233
Total	4189	(15)	3555	(12)	21292	(73)	29036

RESULTS

The number of registered children with AOM and the number of episodes of AOM diagnosed in each age class in Malmö in 1977-1980 are given in Table IV. In the first year (1977) 1 940 episodes of AOM were registered in 1 543 children. In the following years, the corresponding figures were higher, mainly because of inclusion of one or more age classes. They were also higher in 1980 than in 1979 in comparable ages. Of the children with AOM in 1980 when 15 age classes were included, 81 % (2970/3649) were in pre-school age (≤ 6 years).

Table V gives the number of children with AOM and episodes of AOM in relation to the whole population of children in each year. In 1977, 16 % of the children had at least one episode of AOM. The number of diagnosed episodes per 100 children at risk (attack rate) was 20.6.

Of the children who had episodes of AOM in each of the 3 years studied, 52-55 % (mean 54 %) were boys. The corresponding distribution for the numbers of episodes were 54-56 % (mean 55 %).

Figure 3 illustrates the number of episodes per 100 children at risk in each age class and the distribution of children (%) in each age class who had at least one episode of AOM a year. The largest number of episodes, 30-44 per 100 children at risk, was seen in 1-year-old children. The percentage (22-29 %) of children with AOM was also highest in this age class. Above this age the proportion of children with AOM as well as the number of episodes of AOM successively decreased (1980).

Figure 4 gives the distribution (%) of AOM among different diagnostic units in 1980. All together 61 % of the episodes were diagnosed at the ENT-department, 25 % at the Pediatric department, 10 % by the doctors on duty, and 4 % by other doctors. The age distribution of the patients among the diagnostic units was similar in the other years of registration. Most cases in children under 2 years of age were diagnosed at the Pediatric department, while AOM in older children was mainly diagnosed at the ENT-department.

The distribution of AOM showed a seasonal variation (Fig. 5). In 1977, 1978 and 1980 the greatest number of episodes were noted in December. In 1979 most episodes were registered in April. The

Table IV. *Number of children diagnosed with AOM and number of diagnosed episodes in each age class in 1977 - 1980.*

Age class	Year of registration			
	1977		1978	
	children	AOM	children	AOM
0	443	540	434	550
1	524	707	553	809
2	362	446	349	468
3	214	247	357	427
4			187	229
5				
6				
7				
8				
9				
10				
11				
12				
13				
14				
15				
Total	1543	1940	1880	2483
			2187	2904
			3649	4603

Table V. *Children with AOM and number of episodes in relation to the total number of children*

Year	Age classes	Total no. of children	Children with AOM		Diagnosed episodes of AOM	
			No.	%	No.	Rate per 100 at risk
1977	0 - 3	9397	1543	16	1940	20.6
1978	0 - 4	11412	1880	16	2483	21.8
1979	0 - 5	13452	2187	16	2904	21.6
1980	0 - 15	37347	3649	10	4603	12.3

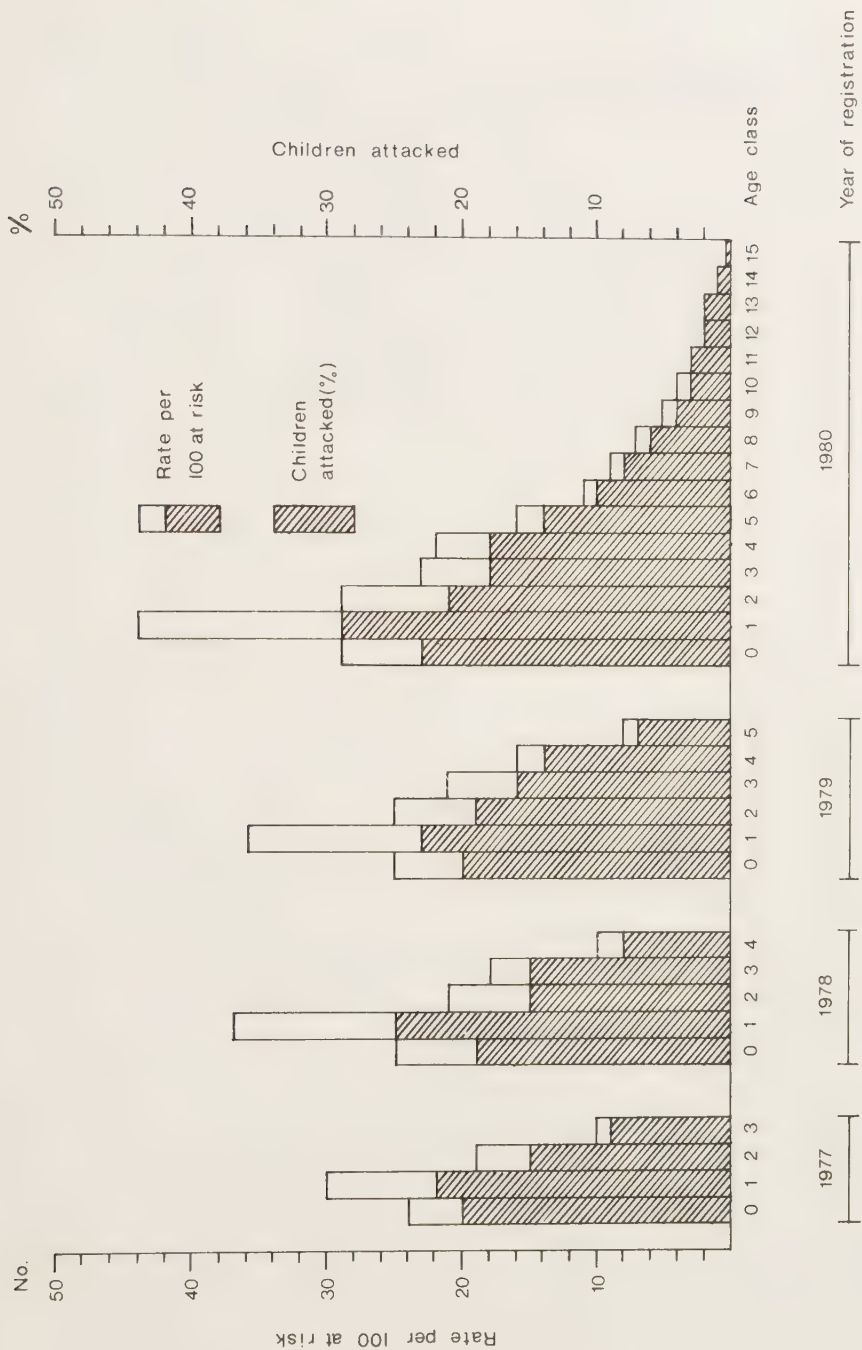


Fig. 3. Number of episodes of AOM per 100 children at risk and proportion of children (%) attacked.

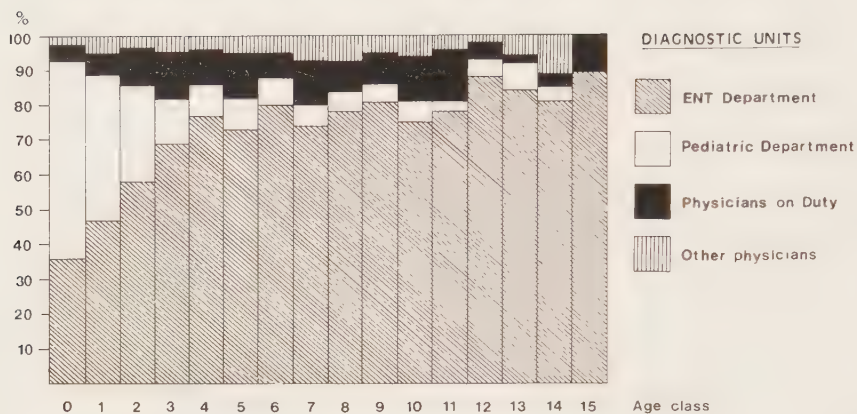


Fig. 4. Distribution of AOM between different diagnostic units.

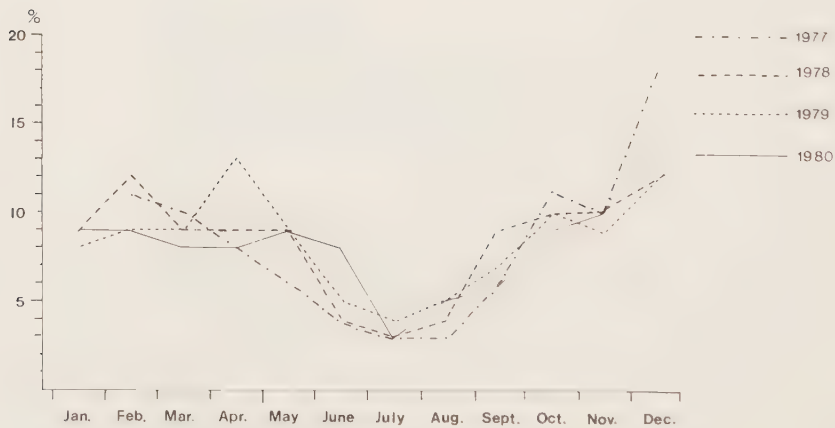


Fig. 5. Seasonal variation in the occurrence of AOM in children.

smallest figures were seen in June, July and August each year.

The occurrence of AOM in children living in different districts is given in Table VI. During the first 3 years of registration the distribution of children with AOM as well as the number of episodes of AOM per 100 children at risk per year differed between the districts. Of all the children living in the centre of the city (districts 11-13), 9 % had at least one episode of AOM in 1977. The children in the centre of the city had, on the average, 11.6 episodes per 100 children at risk. The corresponding figures for children living in the villa suburb Oxie (districts 30-32) were 22 % and 28.5 AOM per 100 children at risk, respectively. Clear differences were found between these two districts also in 1978 and 1979. In 1980 these differences disappeared because of a smaller number of AOM in children over 6 and 7 years of age (Tables II, IV and Fig. 2).

Figure 6 compares the distribution between different kinds of day-care in the children with AOM at the time of diagnosis and the

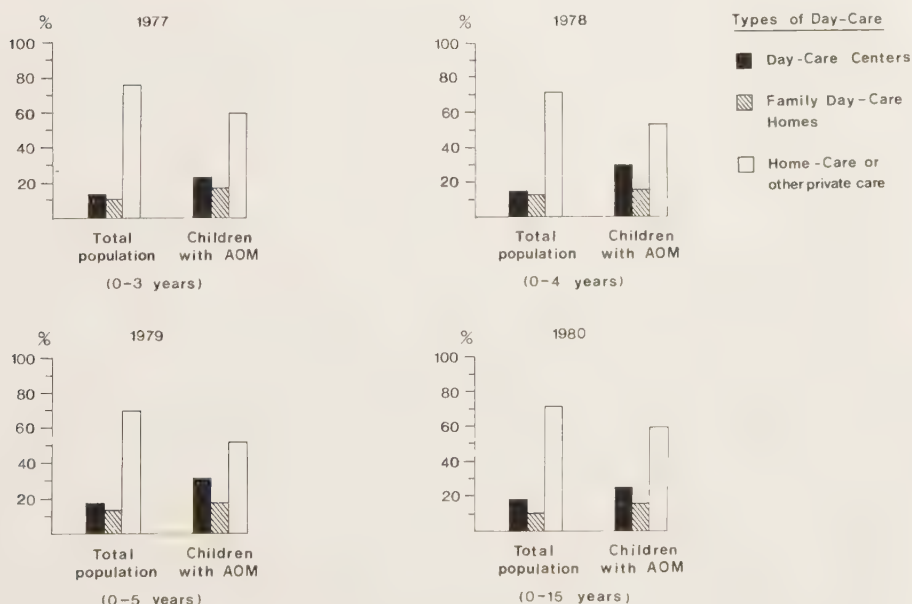


Fig. 6. Distribution between different types of day-care in the population and in children with AOM.

Table VI. Occurrence of AOM in children living in different districts in Malmö 1977 - 1980

District	1977 (0-3 years)		1978 (0-4 years)		1979 (0-5 years)		1980 (0-15 years)	
	Children with AOM %	Rate per 100 at risk	Children with AOM %	Rate per 100 at risk	Children with AOM %	Rate per 100 at risk	Children with AOM %	Rate per 100 at risk
11-13	9	11.6	13	17.3	12	14.7	9	10.7
14	11	13.2	12	16.9	15	19.8	9	11.5
15	15	16.5	13	18.3	13	17.3	8	8.8
16	14	19.1	14	19.0	15	20.6	10	12.5
17	15	18.6	15	19.8	18	24.9	11	14.5
18	14	17.1	14	18.2	15	19.3	9	10.7
20-22	14	17.1	16	21.9	18	25.7	9	11.5
30-32	22	28.5	20	27.0	16	21.4	9	11.3
Total	14	17.2	14	19.2	15	20.2	9	11.6

corresponding distribution in the same age classes of the total population. All together 13-18 % of all children were registered at day-care centers within the city during the years in question. Of the children with AOM, 23-31 % were dwelling in day-care centers at the time of the diagnosis. The distribution of the children with AOM among different types of day-care differed significantly from that in the total population during all the four years of registration ($p < 0.001$).

Table VII shows the number of AOM per 100 children at risk in relation to type of day-care. During the first 3 years of registration most episodes of AOM per 100 children at risk occurred in children in day-care centers. The smallest number of AOM occurred in children cared for at home or in other private care. The figures seen in 1980 are not comparable since children over 11 years of age are not entitled to public day-care.

DISCUSSION

AOM is one of the most common bacterial complications of upper respiratory tract infections in children. The etiology, diagnosis and treatment of AOM have been widely investigated, but the epidemiology has not received the same interest. According to Kudrjavcev & Schoenberg (1979) many of the earlier epidemiologic studies differ essentially from one another. Prospective longitudinal cohort studies in a geographically defined population are, as far as we know, not available. Studies where factors at risk are identified and analysed are very few.

In earlier epidemiologic studies in children the occurrence of AOM has been investigated mainly in relation to age, sex and seasonal variation (MRC, 1957; Paavolainen, 1967; Brownlee et al., 1969; Lowe et al., 1969). The significance of race and/or socio-economic factors has been investigated in some studies (Cambon et al., 1965; Paterson & MacLean, 1970; Vinther et al., 1979; Teele et al., 1980; Vinther et al., 1981).

Malmö is well suited to epidemiologic studies. The population is well defined, each individual is data-registered and can be identified. Standard of dwelling conditions in the city are well

Table VII. *Number of AOM per 100 children at risk in relation to different types of day-care*

Type of day-care	Rate per 100 at risk			
	1977 (0-3 years)	1978 (0-4 years)	1979 (0-5 years)	1980 (0-15 years)
Day-care centers	36.5	41.1	37.5	17.0
Family day-care homes	32.0	26.2	26.2	19.9
Home-care or other private care	16.3	15.9	15.5	10.1

documented. All children living in the city are registered from birth up to 11 years of age according to type of day-care. There is only one hospital and a limited number of doctors in public and private practice working outside the hospital. All the above-mentioned factors contributed to the realization of the present epidemiologic study. Computerized collection and analysis of the material made the project technically feasible. When planning the study we had no specific data of the number or age distribution of episodes of AOM in children living in the city. In the first year of registration when the organization of the study and computer programme was to be tested, it was decided to include only children up to 3 years of age in order to avoid too large and unwieldy a material from the start. In 1980 the investigation was extended to include all children up to 15 years of age as the project had proceeded in an acceptable way.

The present registration of episodes of AOM reflects the clinical diagnosis made by the individual doctors. Thus, the study may include interindividual differences in diagnostic skill and experience between the doctors. Therefore, the registration does not take into account any over- or underdiagnosis. Nor is it possible to form a certain opinion on the number of concealed episodes of AOM, i.e. cases never seen by a doctor.

In the first year 1 940 episodes of AOM were registered in 1 543 children (Table IV). During the following years the number of children with AOM increased as well as the total number of episodes, primarily because of inclusion of one or more age classes. The quantitative increase in the number of children and diagnoses in all comparable age classes seen in 1980 (Table IV) could be explained mainly by the fact that the doctors at the emergency unit outside the hospital and the ambulatory doctors on duty were included in the organization. The annual increase observed during 1978-1980 in the highest age class each year may be explained partly by technical improvements of the registration concurrently with successive expansion of the organization. Thus, since 1980 the system covers the greatest possible number of cases of AOM in children living in Malmö and also gives a clear picture of the age distribution. More than 80 % of the cases occurred in pre-school children. Corresponding distributions have been reported by other investigators (MRC, 1957; Paavolainen, 1967; Lowe et al.,

1963).

An equal sex distribution of AOM between boys and girls has been reported in some earlier investigations (MRC, 1957; Lowe et al., 1963). However, in most other studies the occurrence of AOM has been found to be higher in boys than in girls (Nielsen, 1945; Feingold et al., 1966; Reed et al., 1967; Eldridge et al., 1970). In our study more boys than girls had AOM. But this corresponded to a larger number of boys in the population and the sex difference was not significant.

In two investigations from England, Lowe et al. (1963) as well as Paterson & MacLean (1970) registered the number of episodes of AOM during one year in about 2 000 children up to 15 years of age. In their studies 6 and 11 % of the children had at least one episode of AOM. The present study showed that about 10 % of the 37 347 children up to 15 years of age had at least one episode of AOM in 1980.

Feingold et al. (1966) and Brownlee et al. (1969) found the greatest distribution of AOM in 1- and 2-year-old children. In a British study (MRC, 1957), the highest occurrence was registered in the ages between 3 to 6 years with a peak at 6 years of age, while Lowe et al. (1963) registered the highest occurrence before the age of 1 and a smaller peak at 5-6 years of age. Most investigators reported a rapid decrease in the occurrence after the age of 6. In our study AOM was most common in 1-year-old children, 29 % of them had at least one episode of AOM in a year (1980). After the age of 1 year the occurrence of AOM decreased rapidly, and after the age of 6 the annual occurrence was less than 10 % of the population. The present study also clearly demonstrates that the number of episodes were highest in 1-year-old children.

Most episodes of AOM were diagnosed at the ENT- and Pediatric departments. Children under 2 years of age were primarily diagnosed at the Pediatric department. This is probably because the symptoms at this age are so unspecific that the Pediatric department was primarily contacted. Older children could describe their ear symptoms and the ENT-department was therefore contacted to a greater extent.

The seasonal variation with most episodes of AOM from October-November to March-April with a peak in December corresponds to

that found in earlier studies (MRC, 1957; Lowe et al., 1963) and the occurrence of AOM can be expected to follow the seasonal variation of viral upper respiratory tract infections (Fry, 1961). Every winter AOM is less common in January compared to December. This may be due to the fact that one or more age classes were not registered during January 1978-1980 (see page 3, B. Registration). It may also be due to the diminished exposure to upper respiratory tract infections in children during the Christmas holidays, i.e. 2-3 weeks from the end of December till the beginning of January when many children are at home. Each year the smallest number of episodes of AOM was diagnosed in the summer months, June-August. This probably meant a true decrease in the occurrence of the disease. However, many children leave the city to stay at other places for the summer, which may help to explain the observed decrease in the occurrence of AOM.

The occurrence of episodes of AOM in children varied between the districts. In the first 2 years of registration the highest figures were found for children living in a modern villa suburb (Oxie), while the lowest figures were constantly noted in children living in elderly apartment houses of mixed, but mostly good standard, in the centre of the city. Vinther et al. (1981) found that the frequency of AOM varied with the type of house in which the children were living. AOM was more common among children in modern concrete apartment-houses than those living in older brick houses.

The attack rate of AOM varied with the type of day-care. The occurrence was higher in children attending day-care centers than in home-care, while those in family day-care homes held an intermediary position. The daily and intimate contact with other children might perhaps explain the increased occurrence of AOM in children in day-care centers. However, this might also be due to different age distribution between the different types of day-care. Strangert (1976) found AOM to be more common among children in day-care centers than in home-care or in family day-care homes. Similar findings have been reported by Vinther et al. (1979). Ståhlberg (1980) also reported a higher frequency of upper respiratory tract infections and AOM among children in day-care centers.

The present prospective longitudinal study of AOM in children

was possible thanks to the unique conditions existing in Malmö, to the uniform design of the project and to the computer technique. The occurrence of AOM was highest among 1-year-old children and did not vary significantly with sex. Seasonal variation, differences in the occurrence of AOM among children living in different districts and differences according to type of day-care were found. The material will be analysed further in a cohort study, where the incidence of AOM will be studied in relation to different demographic and social factors.

ZUSAMMENFASSUNG

Seit 1977 werden von uns in einer prospektiven epidemiologischen Langzeitstudie sämtliche in der Stadt Malmö, Schweden, wohnhaften Kinder registriert, die an einer ärztlich diagnostizierten akuten Mittelohrentzündung erkrankt sind. Die Registrierung umfasst ausser den Geburtsdaten Angaben über die Anschrift und Tagespflege der Kinder. Die Registrierung 1977 umfasste alle Kinder im Alter bis zu 3 Jahren. Die in den folgenden 2 Jahren neugeborenen Kinder wurden in die Untersuchung einbezogen und seit 1980 werden sämtliche Kinder bis zu 15 Jahren registriert.

Die Krankheit trat am häufigsten bei einjährigen Kindern auf, von denen 29 % wenigstens einmal im Jahr erkrankten. In der Häufigkeit bestand kein Unterschied zwischen den Geschlechtern. Die Mehrzahl der Krankheitsfälle trat in den Wintermonaten ein. Die Krankheit war bei Kindern aus einem modernen Villenviertel am Rande der Stadt häufiger als bei Kindern, die im Stadtzentrum wohnhaft waren. Die in Kindertagesstätten betreuten Kinder wiesen eine höhere Erkrankungsrate auf als die zuhause betreuten Kinder.

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L. Ingvarsson, M.D.
Dept. of Otolaryngology
University of Lund
Malmö General Hospital
S-214 01 Malmö
Sweden

A PROSPECTIVE STUDY OF ACUTE OTITIS MEDIA IN CHILDREN
2. INCIDENCE IN AN URBAN POPULATION

Leif Ingvarsson¹, Kaj Lundgren¹, Bertil Olofsson² and
Stig Wall³

*From the ¹Department of Otolaryngology, University of Lund,
Malmö General Hospital, Malmö, and the ²Department of Mathematical
Statistics, Institute of Technology, University of Lund, Lund,
and the ³Department of Preventive and Social Medicine, University
of Umeå, Umeå, Sweden*

Abstract. Since 1977 a cohort study on the incidence of acute otitis media (AOM) is going on in Malmö, Sweden. The study includes 8 900 children born in 1977-1980. The maximum time of observation was 48 months. Children, aged 6-11 months, run the greatest risk of getting AOM. 54 % of the children born in 1977 had at least one episode before the age of 48 months and 48 % of these children had more than one episode. There was no difference with sex, but the boys had significantly higher cumulative incidence rate (CIR) than the girls. Recurrent episodes were significantly higher in children having their first episode before the age of 18 months. The CIR of AOM was higher among children in a modern villa suburb compared to those in a modern apartment-house district or in the centre of the city. Children at day-care centers run a greater risk of getting recurrent AOM than those at home or in family day-care homes.

The epidemiology of Acute Otitis Media (AOM) in children is still to a great deal inadequately explored (Hinchliffe, 1972; McEldowney & Kessner, 1972; Manning et al., 1974; Kudrjavcev & Schoenberg, 1979). Among earlier epidemiologic studies there are very few cohort studies penetrating the relation between AOM and demographic and socio-economic factors. Furthermore, such studies have been more or less selected. Prospective investigations in a sufficiently large cohort of unselected children from a well defined population have been recommended (McEldowney & Kessner, 1972; Kudrjavcev & Schoenberg, 1979).

Malmö is a well defined geographic unit with unique conditions for epidemiologic studies (Sternby, 1968; Isacsson, 1972; Janzon, 1974; Lannerstad, 1978; Ingvarsson et al., 1982). The aims of the present investigation have been:

- to perform a descriptive study of the incidence of AOM in birth cohorts of children born in 1977-1980; and
- to analyse the possible influence of different demographic and social factors on the observed incidence of AOM.

MATERIAL

Since 1977 all cases of AOM among children living in Malmö and otoscopically diagnosed by a doctor, have been registered in a prospective epidemiologic study (Ingvarsson et al., 1982). The present cohort study which will continue for a 10-year-period includes at present all children born between the beginning of 1977 and the end of 1980. This means that the children were followed up from birth until December 1980 - the present end-point - implying a maximum of 48 months of observation. Every age class constitutes a separate birth cohort. Thus, children born in 1977 have the longest time of observation and the principal part of the results refers to this cohort.

STATISTICAL MANAGEMENT

One measure of the occurrence of AOM was used in the analyses:

- the time interval between birth and the first episode of AOM (Incidence Rate of the first episode of AOM).

The Cumulative Incidence Rate (CIR) has been calculated from the age-specific incidence rates with the life-table method. This means that all individuals in a population can be included in the calculations, even if they differ in duration of observation. Each individual contributes "risk time" (person-months of follow-up) until the first AOM is diagnosed or until the study end-point. This method is frequently used in different types of studies of survival. For technical details, see Appendix. Comparisons of different statistical distributions were made with the χ^2 -analysis. All data were processed according to a special computer programme (Persson, 1981).

POPULATION

Every year each birth cohort slightly changed due to people moving into or out of the city as well as possible deaths. With regard to these changes corrections of the respective cohorts were required for the calculations of the results. Such corrections are exemplified below for children born in 1977.

In 1977 totally 2 415 children (1 280 boys and 1 135 girls) were born in the city of Malmö. During that year the number of children decreased owing to more people leaving the city than moving into it. At the end of the year, the number of remaining children was 2 266 children (1 201 boys and 1 065 girls). A net decrease of the cohort was noted also in 1978, 1979 and 1980. The net changes during the whole period of observation, 1977-1980, and the mean value calculated for the cohort of children born in 1977 are given in Table I. The mean value was used as an estimate of the size of the population at risk, subject to life-table analyses. Corresponding calculations were performed for the other cohorts of children born in 1978, 1979 and 1980, respectively. Mean values and sex distribution of the children are given in Table II.

Corresponding mean values of the number of children living in different dwelling districts were calculated. Official population statistics from the city of Malmö were used.

Table I. *Number of children born in 1977 and living in Malmö from 1977 to 1980*

	No. of children at the respective date				Mean
	Jan 1st 1978	Jan 1st 1979	Jan 1st 1980	Jan 1st 1981	
Boys	1201	1167	1152	1124	1166
Girls	1065	1035	1022	996	1025
Total	2266	2202	2174	2120	2191

Table II. *Mean values and sex distribution of children in Malmö born 1977 - 1980*

	Year of birth							
	1977		1978		1979		1980	
	No.	%	No.	%	No.	%	No.	%
Boys	1166	53	1128	51	1165	52	1174	52
Girls	1025	47	1083	49	1075	48	1101	48
Total	2191		2211		2240		2275	

Public child-care

The public child-care service includes mainly two types of day-care; *viz.* day-care centers and family day-care homes. Children not looked after by the public child-care are cared for at home or by private child-minders. The different forms of child-care in different ages have been exemplified in a previous report (Ingvarsson et al., 1982).

DEFINITIONS

Cohort = a well defined group of people with some given characteristic(s) in common.

Population at risk = number of children exposed to the risk of getting AOM

Incidence Rate of the first episode of AOM = $\frac{\text{number of children getting their first episode of AOM}}{\text{Population at risk}}$ per time unit

Cumulative Incidence Rate (CIR) = $\frac{\text{number of children getting AOM during a specified period of time}}{\text{number of children in the population at the beginning of the period}}$

CIR is expressed in percentage.

RESULTS

The number of children with AOM, born in 1977-1980 and living in Malmö, and the number of episodes of AOM during the same period are given in Table III. Of the 2 191 children born in 1977, 617 (56 %) boys and 484 (44 %) girls had respectively 1 275 (58 %) and 937 (42 %) episodes of AOM.

Year of birth

The age-specific incidence rates (per 1000 months follow-up) of the first episode of AOM given in half-year-intervals for all cohorts (children born in 1977-1980) are given in Table IV. The highest incidence of AOM was noted in the age interval 6-11 months for all 4 cohorts. The figures were comparable in corresponding age intervals and there were no significant differences between the 4 birth cohorts indicating a fairly consistent incidence pattern. For simplicity, therefore, the following results refer mainly to the birth cohort of children born in 1977.

Table III. *Number of children with AOM and number of episodes of AOM in children born in 1977 - 1980*

	Year of birth											
	1977			1978			1979			1980		
	Children		AOM	Children		AOM	Children		AOM	Children		AOM
	No.	%		No.	%		No.	%		No.	%	
Boys	617	56	1275	58	534	54	1061	56	416	57	721	58
Girls	484	44	937	42	458	46	837	44	312	43	516	42
Total	1101		2212		992		1898		728		1237	
										197		255

Table IV. *Age-specific incidence rate (per 1000 months' follow-up) of the first episode of AOM in children born in 1977 - 1980*

Age interval (months)	Year of birth			
	1977	1978	1979	1980
0 - 5	5.4	5.3	5.7	5.9
6 - 11	32.3	28.0	28.1	26.4
12 - 17	20.9	24.4	23.4	
18 - 23	14.9	20.3	24.2	
24 - 29	14.5	14.2		
30 - 35	12.2	21.0		
36 - 41	10.8			
42 - 47	13.6			

Age and sex

The age-specific incidence rate of the first episode of AOM in children born in 1977 is given in Table V. The highest incidence rate (greatest risk of getting AOM) was found in the age interval 6-11 months for both boys (36.0) and girls (28.1).

The cumulative incidence rate (CIR) of AOM, calculated from the age-specific incidence rates, in boys and girls is illustrated in Fig. 1. At the age of 12 months, 22 % of the boys and 19 % of the girls had had at least one episode of AOM. At the end of the observation period, 48 months, 56 % of the boys and 53 % of the girls were estimated to have had their first episode of AOM. The cumulative incidence rate for boys and girls of comparable ages differed significantly ($p < 0.001$).

The number of episodes of AOM per child in boys and girls and the number of episodes in relation to the time of the first episode, before or after 18 months of age, are given in Table VI. Among the boys and girls with AOM, 49 % and 56 %, respectively, had one episode of AOM, while 13 % of both sexes had 4 or more. There was no difference between boys and girls concerning the number of episodes per child. The relation between number of

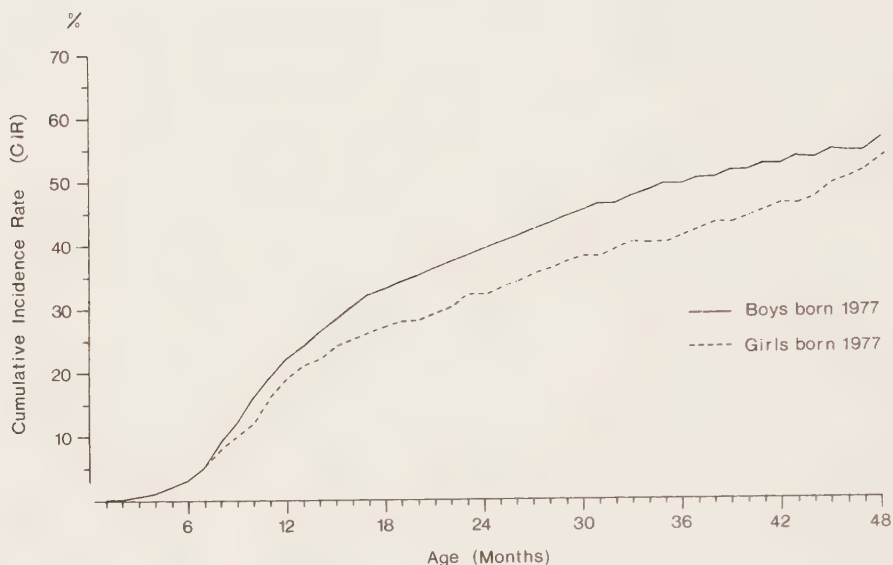


Fig. 1. Cumulative incidence rate (CIR) of the first episode of AOM in relation to sex.

episodes per child and age at the first episode is also illustrated in Fig. 2. Of the children having their first episode of AOM before the age of 18 months, 19 % had 4 or more episodes. The corresponding figure for the children with the first episode after the age of 18 months was 3 %. The risk of getting recurrent episodes of AOM was significantly higher ($p < 0.001$) in children who had their first episode before the age of 18 months.

Seasonal variation

Figure 3 illustrates the seasonal variation during the first 4 years of life (1977-1980). In the first year only a few episodes of AOM were registered during the first 8-9 months. From October 1977 and forwards the number of episodes increased. Most episodes were diagnosed in December each year except for January and April 1979. The number of cases diagnosed was smallest in July and August.

Table V. Age-specific incidence rate (per 1000 months' follow-up) of the first episode of ADM in children born in 1977

Age interval (months)	Boys	Girls	Total	District		
				Oxie	Rosengård	City
0 - 5	5.0	5.7	5.4	6.4	7.7	2.2
6 - 11	36.0	28.1	32.3	41.5	33.8	20.3
12 - 17	24.0	17.5	20.9	31.5	18.8	15.2
18 - 23	16.6	13.1	14.9	17.2	10.7	12.3
24 - 29	15.2	13.7	14.5	19.3	12.1	9.0
30 - 35	14.5	9.9	12.2	15.5	9.9	8.9
36 - 41	9.9	11.7	10.8	13.4	9.4	6.2
42 - 47	9.4	18.1 [*]	13.6 [*]	49.0 [*]	6.9	7.5 [*]

* See discussion

Table VI. Number of episodes of AOM per child in relation to sex and to the time (before or after 18 months of age) of the first episode

No. of episodes per child	Children born 1977				Age at the first episode of AOM			
	Boys		Girls		Total		< 18 months	
	No.	%	No.	%	No.	%	No.	%
1	304	49	273	56	577	52	256	39
2 - 3	233	38	151	31	384	35	279	42
4 - 5	57	9	42	9	99	9	86	13
6 - 11	23	4	18	4	41	4	40	6
Total	617		484		1101		661	
							440	

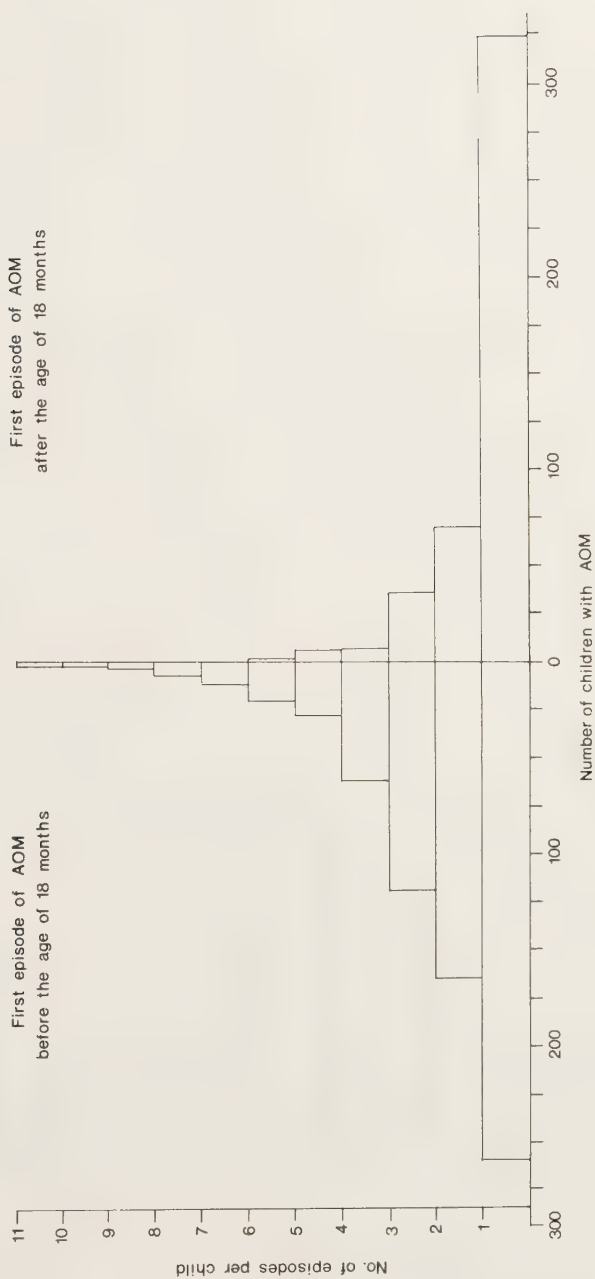


Fig. 2. Relation between number of episodes of AOM per child and age at the first episode.

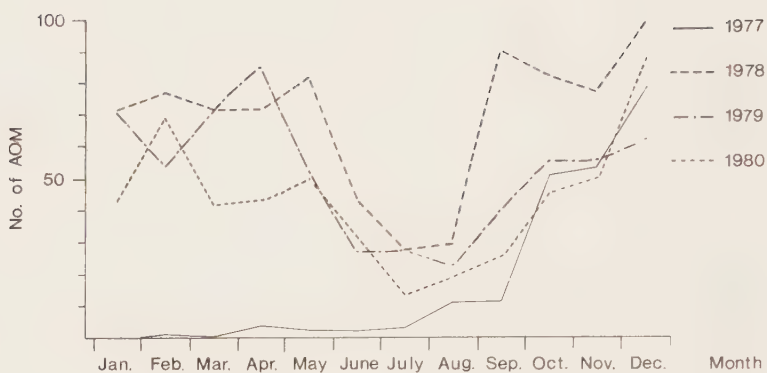


Fig. 3. Seasonal variation of AOM during the first four years of life in children born in 1977.

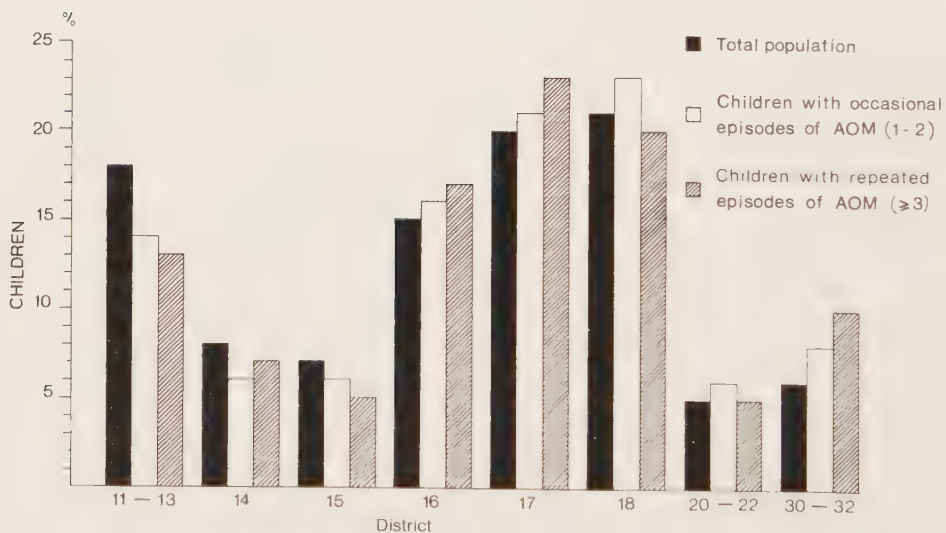


Fig. 4. Distribution of children born in 1977 living in different districts in Malmö in 1977-1980.

Dwelling districts

Figure 4 illustrates the distribution of the cohort among different dwelling districts in Malmö and the corresponding distribution of children with occasional (1-2) and repeated (≥ 3) episodes of AOM. Of all children, 18 % were living in the centre of the city (districts 11-13), while the corresponding figures in children with occasional and repeated episodes of AOM were 14 % and 13 %, respectively. Totally 6 % of the children were living in the villa suburb Oxie (districts 30-32). Corresponding figures for children with occasional and repeated episodes were 8 % and 10 %, respectively.

The age-specific incidence rates of the first episode of AOM in the children in a few different districts - modern villa suburb (Oxie), modern apartment-house district in Rosengård and centre of the city - are given in Table V. The highest incidence rates were noted for the children in the age interval 6-11 months in all the 3 districts: 41.5, 33.8 and 20.3 in Oxie, Rosengård and centre of the city, respectively.

The corresponding CIR are illustrated in Fig. 5. At the end of the observation period (48 months) about 65 % of the children in Oxie, 49 % of the children in the apartment-house district in Rosengård and 40 % of the children living in the centre of the city were estimated to have had at least one episode of AOM. The CIR differ significantly between the 3 districts ($p < 0.001$).

Day-care

The distribution of the children with AOM among different types of day-care at the time of diagnosis is illustrated in Fig. 6. Of all children with occasional (1-2) episodes of AOM, 26 % were attending day-care centers, 15 % family day-care homes and 59 % were cared for at home or by private child-minders. The corresponding distribution of children with 5 or more episodes of AOM was 40, 16 and 42 %, respectively. The 3 groups differed significantly ($p < 0.001$) in the distribution among the different types of day-care.

The distribution among different types of day-care at the time of diagnosis of AOM in the children living in different districts



Fig. 5. Cumulative incidence rate (CIR) of the first episode of AOM in children born in 1977 living in different districts of Malmö.

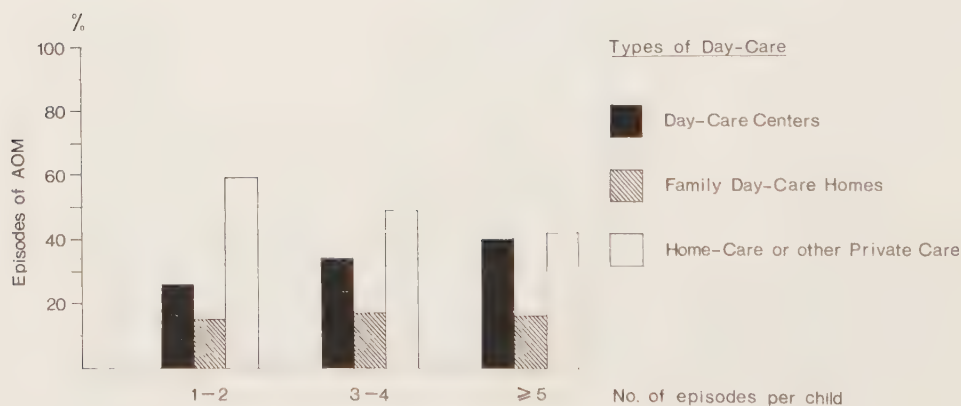


Fig. 6. Distribution among different types of day-care at the time of diagnosis in the children with AOM born in 1977.

is given in Table VII. Of the children with AOM living in the centre of the city (districts 11-13), 37 % were attending day-care centers at the time of diagnosis, 15 % were cared for in family day-care homes, and 48 % were home-cared or in other private care. Approximately the same distribution was found in the other districts.

DISCUSSION

Studies of the incidence of AOM in children with an observation period exceeding one year are very few (Miller et al., 1960; Reed et al., 1967; Kaplan et al., 1973; Teele et al., 1980). However, the groups of children constituting these cohorts are more or less selected. In a review of earlier epidemiologic studies of AOM in children, Kudrjavcev & Schoenberg (1979) pointed out that most studies were deficient in essential respects. Longitudinal prospective studies from geographically defined populations have been recommended (McEldowney & Kessner, 1972; Kudrjavcev & Schoenberg, 1979).

The city of Malmö is a unique area for epidemiologic studies with a well defined population, served by one single hospital.

In the present study, started in 1977, every new-born age class, consisting of about 2 200 children, constituted a separate cohort. Unlike many other studies, there are no restrictions in the selection of children, e.g. caused by social or geographical border-lines in the city.

During the 'seventies the population of Malmö decreased somewhat each year mainly because families with children moved out to the surrounding rural districts. To follow all children individually in the cohorts was impossible and thus, children with AOM moving out of or into the city could not be identified. For this reason, a "mean value" of the size of the cohort was calculated corrected for the changes caused by such removals during the 4 years of observation.

The present study showed that the age-specific incidence rates of the first episode of AOM were very constant in comparable age intervals between the different birth cohorts (Table IV). It was therefore natural to focus the presentation on the children born in 1977, i.e. those observed longest. Thus, the birth

Table VII. *Distribution among different types of day-care at the time of diagnosis in the children with AOM born in 1977 and living in different districts*

District	Type of day-care						Total
	Day-care center		Family day-care home		Home-care or other private care		
	No.	%	No.	%	No.	%	
Centre of the city	97	37	38	15	125	48	260
Rosengård	127	29	67	15	244	56	438
Oxie	59	35	33	20	77	45	169

cohort of the children born in 1977 is the only one analysed in the following discussion.

The life-table method implies that the population decreases successively to a small number of individuals at the end of the observation period. If only some or few additional episodes of AOM occur in the remaining children the last value of the age-specific incidence rates as well as the corresponding CIR-curves will be greatly influenced. Therefore, corresponding "end-results" could be unreliable.

In the birth cohort about 54 % of the children (Fig. 1) were estimated to have at least one episode of AOM before the age of 4 years and of the children with AOM 48 % had more than one episode (Table VI). These figures can be compared with those from the study in Newcastle upon Tyne (Miller et al., 1960), where 19 % of the children had at least one episode before the age of 3, and 30 % of these children had more than one episode. In the Lancet (Editorial, 1970) it is stated that at least a quarter of all children in U.K. have AOM at some time or other.

The cumulative incidence rate (CIR) showed that about 56 % of the boys and 53 % of the girls had got at least one episode of AOM before the age of 48 months (Fig. 1). Even though this end-point difference between the sexes was non-significant, which was also stated in the first report on this epidemiologic study (Ingvarsson et al., 1982), the present study showed that roughly between 12-42 months of age the CIR was significantly higher in the boys than in the girls.

The CIR showed that the risk of having AOM before the age of 6 months was very small. However, in the following age interval, 6-11 months, the children run the greatest risk of getting AOM within their first 4 years of life (Fig.1, Table V). Corresponding figures from other investigations of comparable populations are hard to get since definition of the conditions differed and since the observation time was as a rule shorter.

Howie et al. (1975) retrospectively followed up a group of 488 children from birth up to 5 years of age. The children who had got their first episode of AOM before the age of 18 months were more prone to get recurrent AOM than those having their first episode after this age limit. In the present prospective

study, where 1 101 children in the cohort of 2 191 individuals had at least one episode, the same result was found. The children who had their first episode of AOM before the age of 18 months were significantly more prone to have recurrences than those who had their first episode after the age of 18 months (Table VI, Fig. 2).

The seasonal variation of AOM, described in the first report (Ingvarsson et al., 1982), was also confirmed in the present study. In the cohort of children born in 1977, the occurrence of episodes increased significantly in October. The disappearance of the maternal immunoglobulins and an immature immune defence system as well as increased exposure to upper respiratory tract infection may probably explain the above increase. From October 1977, a seasonal variation was noted throughout the observation period.

Important differences were found in the incidence rate of the first episode of AOM among children living in different districts in Malmö (Table V and Fig. 5). The children living in a modern villa suburb (Oxie) had a significantly higher incidence rate than those living in the apartment-house district (Rosengård) and in the centre of the city. Conceivable causes of the differences found between the districts can be differences in the dwellings and close environments. Most of the children in the centre of the city were living in older apartment-houses, while children in the apartment-house area of Rosengård lived in concrete buildings built in the 'sixties and 'seventies. Most of the children in Oxie lived in modern villas from the 'seventies. Vinther et al. (1981) also found more episodes of AOM in children living in concrete apartment-houses than in those living in older brick apartment-houses.

The type of day-care of the children seems to be associated with the risk of getting AOM during the first 3-4 years of life. The children attending day-care centers had AOM more often than those cared for at home. Children attending family day-care homes occupied an intermediate position. Corresponding differences have been found by other investigators (Strangert, 1976; Vinther et al., 1979; Ståhlberg, 1980). Furthermore, the children attending day-care centers also had the largest number of recurrences. These differences are probably due to the fact that

children dwelling in larger groups, such as day-care centers, more often and more readily transmit upper respiratory tract infections to each other leading to more bacterial complications such as AOM. However, for technical reasons, in the present study, the figures for the distribution of children with AOM among different types of day-care have so far not been age-standardized. Thus, the differences between figures may possibly be somewhat more or less pronounced when this correction has been performed.

The differences in the incidence of AOM found between children living in different districts stated above were not due to differences in distribution between the types of day-care. Of the children living in the centre of the city who had the lowest CIR of AOM, 37 % were cared for in day-care centers. The corresponding figures for the children with AOM in Oxie and Rosengård were 35 % and 29 %, respectively (Table VII).

It was not possible in the present study to investigate other factors probably influencing the incidence of AOM in children. Such factors might be heredity, the degree of immunologic defence, the importance of breast contra artificial feeding to immunologic defence. External factors such as type and quality of housing, degree of air humidity and ventilation in the apartment, "passive" smoking and other air pollutions might also be of interest. The next step in the present epidemiologic study of AOM in children includes an analytic case-control-study, comparing a group of children with recurrent episodes of AOM ("case") with an equivalent group of healthy children ("control"), where etiological factors, exemplified above, are planned to be penetrated.

APPENDIX

The distribution of the time of the first AOM is assumed to be given by the expression

$$F(t) = 1 - \exp\left(-\int_0^t h(u) du\right), \quad t \geq 0$$

Hence, $F(t)$ denotes the probability of having an AOM before time t . The probability of having the AOM in a short interval just after time u is denoted by $h(u)$, the incidence density. The estimation of $h(u)$ was done by first breaking up the total time interval into 30-day-periods. Then $h(u)$ was estimated from the expression

$$h^*(u) = 2D(t) / (N(t) + N(t+30)).$$

$t = 0, 30, \dots, 1410$.

$D(t)$ denotes the number of children having their first AOM in the interval $(t, t+30)$, and $N(t)$ the number of the children who were still under observation and who had not yet had an AOM at time t . The distribution was then estimated from the Cumulative Incidence Rate (CIR)

$$F^*(t) = 1 - \exp\left(-30 \sum h^*(u)\right),$$

$0 < t < 1410$.

The summation should be extended over the terms for which $u \leq t$. Finally, a transformation of time, from days to months, $t' = t/30$, was made. Thus, in this context a month is to be understood as 30 days.

ZUSAMMANFASSUNG

Seit 1977 läuft in der Stadt Malmö, Schweden, eine Kohortenstudie über das Auftreten von akuter Mittelohrentzündung, wobei 8 900 Kinder der Jahrgänge 1977 - 80 erfasst worden sind. Die maximale Beobachtungszeit beträgt z. Zt. 48 Monate. In einem Alter der Kinder von 6 - 11 Monaten erwies sich das Risiko einer Erkrankung am grössten. Im Alter von 48 Monaten hatten 54 % der 1977 geborenen Kinder wenigstens einmal eine Mittelohrentzündung durchgemacht, und von diesen Kindern hatten 48 % die Krankheit mehr als einmal. Geschlechtsabhängige Unterschiede im Auftreten der Krankheit wurden nicht festgestellt. Wiederholte Erkrankungen waren signifikant häufiger bei den Kindern, die ihre erste Mittelohrentzündung schon vor einem Alter von 18 Monaten durchgemacht hatten. Die kumulative Auftrittsrates der akuten Mittelohrentzündung war bei Kindern aus einem modernen Villenviertel am Rande der Stadt höher als bei Kindern, die in einem Bezirk mit modernen Mietshäusern oder im Stadtzentrum wohnten. Die Gefahr einer wiederholten Mittelohrentzündung ist bei den in Kindertagesstätten betreuten Kindern grösser als bei den Kindern, die entweder in der eigenen oder in einer fremden Familie betreut werden.

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L. Ingvarsson, M.D.
 Dept. of Otolaryngology
 University of Lund
 Malmö General Hospital
 S-214 01 Malmö
 Sweden

ACUTE OTALGIA IN CHILDREN – FINDINGS AND DIAGNOSIS

LEIF INGVARSSON

From the Department of Otolaryngology, University of Lund, Malmö General Hospital, Malmö, Sweden

ABSTRACT. Ingvarsson, L. (Department of Otolaryngology, University of Lund, Malmö General Hospital, Malmö, Sweden). Acute otalgia in children—findings and diagnosis. *Acta Paediatr Scand*, 71, 1982.—One hundred and seventy-one children up to 15 years of age and with acute otalgia were examined to find out whether otalgia or any other symptoms were so closely related to acute otitis media (AOM) as to make otoscopic examination unnecessary. AOM was diagnosed in 46%, simplex otitis in 15%, serous otitis media (SOM) in 17%, and normal eardrums in 22%. Children with AOM had fever and spontaneous perforation of the eardrums in 78% and 30% of the cases, respectively. Of the children who had not AOM (54%), the otalgia could in most cases be classified as referred pain due to, for instance, discomfort when swallowing, nasal obstruction or throat pain. Other reasons were general irritability due to fever, teething or moderate hearing loss. The difficulties in diagnosing AOM simply on the basis of symptoms were demonstrated in the investigation. Symptoms such as otalgia, otorrhea, fever or upper respiratory tract infection (URI), possibly except for the combination of otorrhea and fever, can occur without AOM. A correct otoscopic examination and evaluation of the eardrums is necessary in children with otalgia, other symptoms of URI or in doubtful cases of acute illness. Physicians without possibilities to evaluate the eardrums properly should thus refer the patient to an otologist without delay.

KEY WORDS: Acute otitis media, children, diagnosis, otalgia, otomicroscopic examination, serous otitis media, simplex otitis

Acute otitis media (AOM) is one of the most frequently occurring complications to upper respiratory tract infections (URI) in childhood. The main symptoms are ear-ache (otalgia), fever and occasionally otorrhea. However, AOM can occur without otalgia or fever, just as these symptoms do not necessarily mean AOM. Thus, the clinical symptoms of AOM vary and are unspecific and sometimes directly misleading, for which reason a firm diagnosis requires visualization of the eardrums (1–8).

Children with otalgia are often examined by pediatricians or general practitioners with varying experience and ability to examine the eardrums properly. As the otoscopic examination may be difficult owing particularly to the narrowness of the ear canal, especially in small children, the risk of an incorrect diagnosis increases with the lack of experience and otoscopic skill of the examiner. In cases

where the eardrums are difficult to examine, the diagnosis of AOM is therefore often based only on symptoms of otalgia, fever and/or URI or any other symptom (8).

The aim of the present investigation was to find out whether otalgia or other symptoms were so closely associated with AOM as to make otoscopic examination unnecessary in the diagnosis of the condition.

MATERIAL AND METHODS

The clinical material consisted of 171 children up to 15 years of age and seen at the ENT Department of Malmö General Hospital because of otalgia and suspected AOM. The investigation took place from November 1978 to January 1979. Children who had had middle ear diseases or had been treated with antibiotics during the preceding 4 weeks were excluded from the investigation. Otalgia was reported by the patients and/or by the parents owing to changes observed in the children (e.g. crying, irritability, ear tugging, tragus tenderness or otorrhea). The preliminary history was obtained by an experienced nurse, after which the children were examined by a

Table 1. *Age and sex distribution of children with otalgia*

Age	♂	♀	Total	%
0-1	26	18	44	26
2-3	25	13	38	22
4-5	13	16	29	17
6-7	17	9	26	15
8-15	17	17	34	20
Total	98 (57%)	73 (43%)	171	

trained otologist within 3 or 4 hours. Examination included inquiry about the duration of otalgia, fever, any co-existing URI and signs of otorrhea. The complete ENT-examination consisted of otoscopic and otomicroscopic investigation of the eardrum including contour, translucence, colour, light reflex and mobility. Any signs of disease of the nose, oral cavity, pharynx and larynx of acute infectious character, such as rhinitis, pharyngitis or tonsillitis, were noted. These conditions are hereinafter referred to as URI. Fever refers to a rectal body temperature of at least 38°C.

Definitions

The otomicroscopical criteria for classification of the conditions were as follows:

1. *Acute (purulent) otitis media (AOM)*: reddened, bulging eardrum with otomicroscopical signs of middle ear effusion and impaired mobility or spontaneous perforation and otorrhea.

2. *Otitis media without effusion (simplex otitis)*: reddened eardrum in neutral position without otomicroscopical signs of middle ear effusion and with normal mobility.

3. *Serous otitis media (SOM)*: greyish or lightly vascular eardrum, retracted or in neutral position with otomicroscopical signs of middle ear effusion and impaired mobility.

4. *Normal eardrum (normal)*: greyish, thin eardrum in neutral position with otomicroscopical signs of air-filled middle ear space and normal mobility.

Treatment and controls

Seventy-three children with AOM were treated with the potassium salt of penicillin V and 6 children with erythromycine. All the children also received a nasal decongestant (oximetazolin) and, if necessary, analgetics. Children with simplex otitis (25) or SOM (30) were given a decongestant, but not antibiotics. Children with normal eardrums but with signs of URI were treated according to the findings. All the children with AOM and simplex otitis were re-examined within 10 and 2-5 days, respectively, after the first examination. The children were then examined again after a further 3 weeks and, when indicated, also on later occasions. All the children were followed up for at least 3 months. At the first visit the patients/parents were carefully instructed to contact the otologist if the symptoms of otalgia continued or became worse. This could be done at any time of the day or night on a separate telephone line.

RESULTS

The age and sex distribution of the 171 children is given in Table 1. The group consisted of 98 (57%) boys and 73 (43%) girls.

Eardrum findings. The otomicroscopical findings are given in Table 2. Less than half of the children (46%) were found to have AOM. Of the other children eardrum changes indicating simplex otitis or SOM were seen in 55 (32%). In most cases of AOM, simplex otitis and SOM, signs of URI were found at the ENT-examination. The eardrums appeared normal in 37 (22%) of the children. Of these children, 25 had signs of URI, while the remaining 12 showed no such signs.

Symptoms. The relation between symptoms and otomicroscopical findings is given in Table 3. Most of the children (78%) had had otalgia for less than 24 hours before they were seen at the ENT Department. Anamnestical evidence of URI was described by the majority of the children (82%). The children had generally had such symptoms for more than 48 hours before the clinic had been contacted and had not been brought to the clinic because of them. Fever was noted in 90 (53%) children.

The relation between fever and age among children with and without AOM is shown in Table 4. In this respect the children with AOM differed significantly ($p < 0.001$) from the others (78% compared to 30%). Primarily more than 80% of the children with AOM under 8 years of age were found to have fever. Reports on the duration of fever were most often uncertain. In the majority of the cases body temperature had been measured when the children had started to complain of ear-ache or at the time of contact with the ENT Department.

The frequency of spontaneous perforation with otorrhea in relation to age is given in Table 5. Otorrhea was noted in 24 (30%) of the children with AOM. Otorrhea was found in nearly half of the children (44%) under 2 years of age. Only in 10 of the 24 cases the anamnesis revealed aural discharge.

Table 2. *Otomicroscopical findings in relation to age*

Age	Otomicroscopical findings								Total No.
	AOM		Simplex otitis		SOM		Normal		
	No.	%	No.	%	No.	%	No.	%	
0-1	16	36	1	2	10	23	17	39	44
2-3	19	50	6	16	5	13	8	21	38
4-5	19	65	6	21	2	7	2	7	29
6-7	12	46	6	23	6	23	2	8	26
8-15	13	38	6	18	7	20	8	24	34
Total	79	46	25	15	30	17	37	22	171

All the children with AOM showed different degrees of healing at the first examination within 10 days, but no one was completely healed at that time. Of the 25 children with simplex otitis 2 returned within 24 hours and 1 within 48 hours with symptoms and signs of AOM. These 3 children were treated with penicillin. The rest of the children (22) in this group had normal or nearly normal eardrums at the examination 2-5 days after the first visit. None of these children developed AOM during the next 3 months.

DISCUSSION

In AOM the otoscopic diagnosis can be confirmed by demonstration of pathogenic bacteria in middle ear exudate (5, 7, 9-12). However, sampling of material in the middle ear requires myringotomy, which is not performed by routine in outpatients. In most cases, the

diagnosis is therefore mainly based on symptoms of URI, otalgia, fever, otorrhea and the otoscopic findings.

The results show that AOM was diagnosed in less than half (46%) of the children examined. It is of special interest to analyse the origin of otalgic symptoms among those 54% of the patients (Table 2) who had not AOM. Simplex otitis can be expected to cause pain. However, SOM is usually not combined with otalgia, nor should normal eardrums be painful. The phenomenon of referred pain to the ear must be considered in all cases of otalgia with normal eardrums. Any lesion in the nerve supply areas of the trigeminal, facial, glossopharyngeal, vagus, great auricular and lesser occipital nerves can lead to ear-ache (13, 14). The otalgia must, of course, be considered as a pain referred from the inflamed mucosal linings or the tonsils when URI was present, which was the case in 79% of all the

Table 3. *Symptoms (anamnestical) in relation to otomicroscopical findings*

Otomicroscopical findings	No. of children	Symptoms							
		Otalgia						Fever	
		1-24 h		24-48 h		URI		No.	%
		No.	%	No.	%	No.	%		
AOM	79	65	82	14	18	76	96	62	78
Simplex otitis	25	20	80	5	20	25	100	8	32
SOM	30	21	70	9	30	22	73	6	20
Normal	37	27	73	10	27	18	49	14	38
Total	171	133	78	38	22	141	82	90	53

Table 4. *Fever in relation to age and diagnosis*

Age	AOM			Other cases			Total		
	No.	Fever		No.	Fever		No.	Fever	
		No.	%		No.	%		No.	%
0-1	16	14	88	28	9	32	44	23	52
2-3	19	16	84	19	10	53	38	26	68
4-5	19	16	84	10	3	30	29	19	66
6-7	12	10	83	14	4	29	26	14	54
8-15	13	6	46	21	2	10	34	8	24
Total	79	62	78	92	28	30	171	90	53

children. The symptom called ear-ache by the patient or parents was, on thorough penetration, found to have different reasons. In most cases the otalgia could be classified as referred pain due to discomfort when swallowing (tonsillitis), nasal obstruction or throat pain (pharyngitis). Other reasons were general irritability due to fever, teething or moderate hearing loss (SOM).

The eardrums were found to be normal in 37 children (22%). A "reddened" eardrum was seen especially among the youngest children when they cried or in combination with high fever. Only otomicroscopy could distinguish this "reddening" with certainty from the reddened eardrum seen in simplex otitis. Therefore, such a finding was considered normal and not caused by a middle ear disease.

The origin of the condition described as "simplex otitis" with a reddened eardrum due to hyperemia of the drum and possibly

also the middle ear mucosa but without signs of middle ear effusion, is uncertain. The best way to decide whether middle ear effusion is present or not is to make a myringotomy. Since this was not done in the present investigation, the otomicroscopic evaluation of the position and mobility of the eardrum became more important. The evaluation of the condition was mostly reliable, which was confirmed by the clinical course. The symptoms and signs of simplex otitis disappeared in most cases (22/25) during the next few days. The results thus indicate that cases of simplex otitis are reversible without penicillin therapy.

Whether simplex otitis is due to an inflammatory reaction, seen in URI, or an isolated viral affection, is debatable, but the condition rarely develops into manifest AOM. Otitis media without effusion discussed among leading otologists during the Second International Symposium on Recent Advances in OME, Columbus, Ohio, 1979 (15), is probably referable to "simplex otitis".

It must be of great value to be able to distinguish different kinds of eardrum changes (AOM, simplex otitis and SOM) from normal findings. Careful otoscopy or, even better, otomicroscopy is still the best way to decide whether AOM is present or not.

As the otoscopic examination may be difficult in some cases it is of interest to assess the degree of association between otalgia or additional symptoms and AOM. A close correlation would facilitate the diagnosis and

Table 5. *Spontaneous perforation in relation to age*

Age	Children with AOM	Spontaneous perforation	
		No.	%
0-1	16	7	44
2-3	19	7	37
4-5	19	5	26
6-7	12	3	25
8-15	13	2	15
Total	79	24	30

thus possibly make the difficult otoscopic examination superfluous, especially among the youngest children. The correlation in the different age groups showed as follows.

Children under 2 years of age (44 patients). The investigation showed that in these children otalgia was a most unreliable symptom. As many as 39% had normal eardrums, while only 36% in this group had AOM. Fever was noted in half (52%) of the children in the group. Most of those with AOM (14/16) had fever. Thus, AOM was nearly always associated with fever, while fever, on the other hand, was not a sign of AOM. However, normal body temperature argues against AOM, since only 2 of the 21 children without fever had AOM. Of the group of 44 children, 7 had AOM with spontaneous perforation and otorrhea, and these patients also had fever. Of the remaining 37 children, AOM was seen only in another 9.

The diagnosis of AOM in children under 2 years of age can safely be made without otoscopy only in cases with otorrhea and fever. Otorrhea without fever can be seen in external otitis or in cases with thin fluid cerumen. Of patients with otalgia but without otorrhea, 3 out of 4 cannot be expected to have AOM. This means that every child under 2 years of age and suffering from otalgia must be examined otoscopically.

Children between 2 and 7 years of age (93 patients). The children in this age-group were pooled since there was very little discrepancy between symptoms and findings. Also in this group otalgia proved a very unreliable sign of AOM. However, altogether 87% of the patients had a pathologic eardrum (AOM, simplex otitis and SOM) compared with 61% of the children below 2 years. Of those with AOM, 84% (42/50) had fever. Spontaneously perforated eardrums were seen in 15 children, i.e. every third case of AOM. Also in this age-group co-existing otorrhea and fever indicate AOM with a high degree of certainty but these patients did not constitute more than 16% of all and therefore also in this group

only every sixth child could be diagnosed without otoscopy.

Children between 8 and 15 years of age (34 patients). In this group of children, including 13 (38%) with AOM, correlation between otalgia and AOM was as poor as in the youngest group. Every fourth child had normal eardrums. However, of the 13 children with AOM only 2 had spontaneous perforation and fever, while 4 children had fever without otorrhea.

Only 2 cases in this group could be diagnosed on the basis of otorrhea and fever. The other 32 children had to be examined otoscopically to confirm or to exclude AOM.

The difficulties in diagnosing AOM simply on the basis of symptoms have been illustrated. It is noteworthy that all symptoms, even otorrhea can occur without AOM. Mortimer (6) pointed out that the difficulty in inspecting the eardrum is the main reason why "otitis media is one of the most misdiagnosed conditions of childhood ... overlooked ... as well as ... overdiagnosed". The present investigation shows that a probable diagnosis is warranted only if the patient has otorrhea together with fever. In all other cases an otoscopic examination and a correct evaluation of the eardrum is obviously important for the diagnosis (kind of middle ear disease versus normal status), treatment (antibiotics or not, other therapy) and follow-up of the children. According to current principles in Sweden, antibiotics are indicated only in cases of AOM. However, evaluation of the eardrums can, especially for physicians not trained in otolaryngology be very troublesome. If there are problems to remove cerumen properly or if the appearance and mobility of the eardrum cannot be assessed, there is a risk of an incorrect diagnosis. Physicians without otoscopic experience have to refer the patient to an otologist without delay. This is important especially for the youngest children below 2-3 years of age, in whom AOM is most common and in whom a correct diagnosis is very often difficult to make.

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(L.I.) Department of Otolaryngology
University of Lund
Malmö General Hospital
S-21401 Malmö
Sweden

CONCENTRATION OF PENICILLIN V IN SERUM AND MIDDLE EAR EXUDATE DURING TREATMENT OF ACUTE OTITIS MEDIA

LEIF INGVARSSON, MD

MALMÖ, SWEDEN

CARL KAMME, MD

LUND, SWEDEN

KAJ LUNDGREN, MD

MALMÖ, SWEDEN

Sixty-one patients, aged six months to ten years, with acute purulent otitis media were treated with penicillin V for ten days. The drug was given twice a day in a total daily dose of 50 mg/kg body weight. The concentration of penicillin was determined in serum and in middle ear exudate on one of the first six days of treatment, 60, 120 or 180 minutes after administration of the drug. Bacterial cultures were taken from the nasopharynx before and during treatment and from the middle ear exudate at the time of myringotomy. The serum level of penicillin decreased during treatment. There was also a decrease in penicillin concentration of the middle ear exudate during treatment. This decrease was most pronounced during the first two days. In a few cases *Haemophilus influenzae* was found in the middle ear exudate during treatment. In these cases the concentration of penicillin in the exudate was found to be higher than the mean concentration at corresponding times. The rapid decrease in the exudate concentration of the drug two to three days after the beginning of therapy may suggest that the patients responded to the treatment and that it is the initial concentration that decides whether an infection will respond to the therapy. High exudate concentrations later on seem to be due mainly to a continuation of the inflammatory reaction and had slight or no clinical effect. Thus, the present investigation produced no strong evidence for a ten-day treatment compared with, for example, a five-day treatment.

The therapeutic effect of antibiotics depends on the concentration of the drug at the site of infection. Serum levels after therapeutic doses for all antibiotics are known but the corresponding concentrations at the site of infection have not been studied to the same extent. Acute purulent otitis media is suitable for such assessment and several investigations have been presented on this subject.¹⁻⁴

In a previous investigation the concentration of penicillin V was determined in serum and middle ear exudate in children with acute otitis media after a single dose of either 13 or 26 mg/kg body weight.³ The determinations were performed after the first dose of a ten-day therapy. The highest mean concentration in middle ear exudate after the smaller dose was 2.1 µg/ml and occurred 30 minutes after administration of the drug. After the larger dose the mean concentration in exudate was three times as high, 6.3 µg/ml and was noted 60 minutes after administration of the drug. A dose of 25 mg/kg body weight twice a day was therefore recommended, and this dose has ever since been generally accepted in Sweden.

After equivalent doses, the concentration of penicillin in ear exudate seems to be substantially lower in serous otitis media than in purulent otitis media.⁵ It is therefore reasonable to assume that the exudate concentration of the antibiotic changes in patients responding to therapy as the purulent inflammation abates.

The aim of the present investigation was to deter-

mine the concentration of penicillin V in serum and middle ear exudate and to isolate bacteria in the ear exudate during the course of treatment with penicillin V in acute otitis media in children.

METHODS

The clinical material consisted of 61 patients, aged six months to ten years, with acute purulent otitis media. Forty-four of the patients were under two years of age. The clinical diagnosis was based on the criteria of reddened and bulging tympanic membrane and otoscopic signs of purulent otitis. The patients had not received antimicrobial agents during the last two weeks before entering the study. The children accepted were admitted to the ENT Department of Malmö General Hospital.

Before treatment, a nasopharyngeal specimen was taken for culture. The potassium salt of penicillin V* was given in a dose of 25 mg/kg body weight (mean 25.2, range 19-31) twice a day for ten days. The patients were fasting before receiving the drug. The interval between the beginning of treatment and sampling on one of the first six days of treatment was decided by chance. Only one serum and one exudate sample were obtained from each patient. The samples were collected simultaneously under general anesthesia. The samples were stored at 4°C and assayed within 24 hours as previously described.³ New stock and test solutions of penicillin V were prepared every fourth week. The laboratory staff was unaware of the interval between the beginning of therapy and sampling.

Specimens of ear exudate for bacterial culture were obtained from 53 of the 61 patients. The bacteria were isolated in the conventional way. No attempts were made to isolate cell wall deficient bacteria (L-phase variants). The specimens were kept at 4°C and cultured within two hours.

RESULTS

Figure 1 gives the range and mean values of serum and middle ear exudate concentrations of

*Calcioopen®, AB LEO, Helsingborg, Sweden.

From the ENT Department, University of Lund, Malmö General Hospital, Malmö, Sweden; and the Department of Medical Microbiology, University of Lund, Lund, Sweden.

REPRINTS — Leif Ingvarsson, MD, ENT Department, University of Lund, Malmö General Hospital, S-21401 Malmö, Sweden.

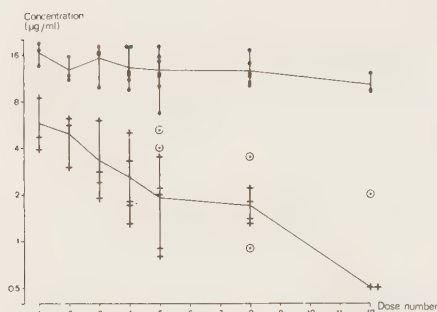


Fig. 1. Concentration (range and mean) of penicillin V in serum (●) and middle ear exudate (+) during the first six days of treatment. Determinations performed 60 minutes after administration of a mean dose of 25 mg/kg body weight (33 patients). ○ - Growth of *H. influenzae* in middle ear exudate.

penicillin V 60 minutes after administration of the drug during the first six days of treatment. The mean serum concentration of penicillin V 60 minutes after the first dose was 16.5 µg/ml. After subsequent doses the mean concentration decreased to 10.2 µg/ml after the 12th dose. The decrease was not statistically significant ($P > 0.05$, Wilcoxon sum range test). The mean exudate concentration of the drug exhibited a decrease from 5.7 µg/ml after the first dose to 0.5 µg/ml after the 12th. The difference between the mean concentration in the early stage of treatment (after the first and second doses) and after the 8th and 12th doses was statistically significant ($P = 0.002$).

Specimens for culture were obtained from 28 of the 33 exudates. *Diplococcus pneumoniae* and *Haemophilus influenzae* were recovered from one and five cases, respectively. No growth was obtained from the other 22 exudates. The exudates yielding growth of *H. influenzae* were markedly purulent and exhibited, with one exception, higher concentrations of penicillin V than the others. They were therefore not included in the calculations of the mean exudate concentration in Figure 1. In one additional exudate yielding growth of a peni-

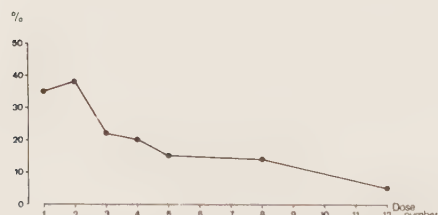


Fig. 2. Relationship between mean concentrations of penicillin V in middle ear exudate and in serum 60 minutes after administration of the drug.

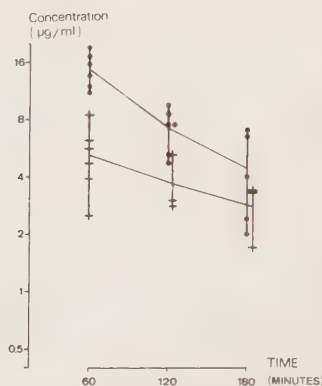


Fig. 3. Concentration (range and mean) of penicillin V in serum and middle ear exudate 60, 120 and 180 minutes after administration of doses 1 and 2 (17 patients). Symbols used are the same as those in Fig. 1.

cillinase-producing *H. influenzae*, the concentration of the drug was below the measurable level (0.5 µg/ml).

Figure 2 shows the mean exudate concentration of penicillin V relative to that of serum 60 minutes after administration. After the first and second doses the mean exudate concentration was 35% and 38% of that in serum, compared with 14% and 5% after the 8th and 12th doses, respectively. The difference was statistically significant ($P = 0.002$).

Figures 3 and 4 give the serum and middle ear exudate concentrations 60, 120 and 180 minutes after administration of the 1st and 2nd doses, and the 8th and 12th doses, respectively. As before, concentrations in exudates yielding growth of *H. in-*

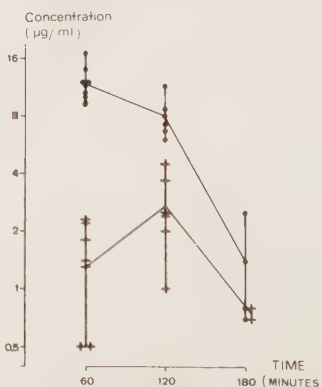


Fig. 4. Concentration (range and mean) of penicillin V in serum and middle ear exudate 60, 120 and 180 minutes after administration of doses 8 and 12 (19 patients). Symbols used are the same as those in Fig. 1.

fluenzae were excluded. After the first two doses the mean serum and middle ear exudate concentrations 60-180 minutes after administration exhibited a decrease corresponding to a half-life of 1.1 and 2.2 hours, respectively. After the 8th and 12th doses the mean serum concentration decrease 60-120 minutes after administration indicated a half-life of approximately 1.8 hours, followed by a rapid decrease with a half-life of approximately 0.4 hour. The mean exudate concentration after the 8th and 12th doses increased to 2.7 µg/ml 120 minutes after administration. This rise was followed by a decrease corresponding to a half-life of approximately 0.6 hour.

The areas under the mean serum and mean exudate concentration curves (area under the curve [AUC] 0-180 minutes) were larger after the first 2 doses than after the 8th and 12th doses. The 0 to 180-minute exudates AUC after the 8th and 12th doses were 44% of that in the first stage of therapy. The difference was statistically significant ($P = 0.002$).

DISCUSSION

After oral administration of drugs in equivalent doses, the serum concentration curve varies due to individual differences in the absorbed amount and rate of absorption of the drug. However, the mean concentrations in serum, 16.5 µg/ml, and in exudate, 5.7 µg/ml, of penicillin V 60 minutes after administration of the first dose in the present investigation were close to those previously reported, 14.5 and 6.3 µg/ml, respectively.³ The decrease in serum concentration of penicillin V during the course of treatment recorded in the present investigation has been reported earlier by other authors.^{6,7}

The longer mean serum half-life 60-120 minutes after administration on the fourth and sixth days of treatment (after the 8th and 12th doses), 1.8 hours, compared with a mean half-life of 1.1 hours in the early stage of treatment may indicate a change in the rate of absorption after some days of treatment. Conclusive evidence of significant differences in absorption rate and/or bioavailability in the early stage of treatment and after some days of treatment requires repeated determinations of serum levels in the same subject. On the fourth and sixth days the 0

to 180-minute area under the mean exudate concentration curve was significantly smaller than in the early stage of therapy. Thus, the bioavailability of penicillin V in the exudate successively decreased as the inflammation in the middle ear abated.

Among the bacteria causing acute otitis media, *H influenzae* has the lowest sensitivity in vitro to penicillin V with MIC-values of 1.20-9.60 µg/ml compared with 0.01-0.04 µg/ml for *D pneumoniae*, the most common agent in otitis media. The large difference in susceptibility to penicillin V was reflected in the isolation rate of the two species from the exudate during treatment. Thus, *H influenzae* was recovered from five and *D pneumoniae* from one of the exudates collected 60 minutes after administration of the drug. Four of the patients with growth of *H influenzae* did not respond satisfactorily to the treatment and their exudates were purulent on the third day of treatment or later. The exudate concentrations of penicillin V in these patients were markedly higher than in patients responding to the treatment, including also patients with *H influenzae* infections.

The rapid decrease in the exudate concentrations of the drug two to three days after the beginning of therapy in patients responding to the treatment may suggest that it is the initial concentration that decides whether an *H influenzae* infection will respond to the therapy. High exudate concentrations later on seem to be due mainly to a continuation of the inflammatory reaction and had slight or no clinical effect. Thus, as far as infections with *H influenzae*, the present investigation produced no strong evidence for a ten-day treatment compared with a five-day treatment.

A clinical trial now in progress indicates that the frequency of unhealed cases is the same after five-day treatment with penicillin V in a dose of 25 mg/kg body weight twice a day as after ten-day treatment with the same daily dose.* These results support the observations made in the present investigation and indicate that exudate concentrations attained after the fifth day of treatment are of slight or no clinical significance in addition to those obtained the first five days of treatment irrespective of etiology.

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PENICILLIN TREATMENT OF ACUTE OTITIS MEDIA IN CHILDREN

A Study of the Duration of Treatment

Leif Ingvarsson and Kaj Lundgren

From the Department of Otolaryngology, University of Lund, Malmö General Hospital, Malmö, Sweden

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Abstract. Two hundred and ninety-seven children, aged 6 months to 7 years, with AOM were treated with penicillin V. One hundred and forty-eight children were given 25 or 50 mg/kg body weight twice a day for 5 days, and 149 children 25 mg/kg body weight twice a day for 10 days. No differences were found in the rate of healing between the 5- and 10-day groups. The larger penicillin dose, which was given to half the 5-day group, did not lead to improved healing. Treatment with penicillin for 5 days instead of 10 does not mean any increased risk of complications such as SOM, relapses, or therapeutic failure. Nor does the risk of a recurrence of otitis increase either. The investigation showed that treatment of AOM with penicillin for 10 days, which is the rule in Sweden, can be reduced to 5 days with maintained satisfactory healing and without risk of increasing the number of complications.

Ever since its introduction in the early 'fifties penicillin V has been used in Sweden as the drug of first choice in the treatment of upper respiratory tract infection and of acute otitis media (AOM). The amount of penicillin V per dose has gradually been increased and today it is generally 25 mg/kg body weight. This dose is based partly upon studies on the concentration of penicillin achieved in the middle ear exudate (Kamme et al., 1969; Lahikainen, 1970).

The administration procedure has been simplified. Since early 'seventies it has been found sufficient to give the above dose twice a day for the treatment of AOM and acute tonsillitis and sinusitis (Edlund et al., 1974; Rundcrantz & Sundför, 1974; Ekedahl et al., 1980). For many years, treatment was continued for 10 days, a routine inherited from the 'fifties

and 'sixties, when the doses used were substantially smaller. However, no efforts have been made to elucidate the effect of the duration of penicillin therapy on the results of AOM.

Kamme et al. (1969) and Lahikainen (1970) studied the penicillin concentration in middle ear exudate in AOM. They found high penicillin concentrations in middle ear exudate during the acute purulent stage of AOM. However, in the same study, Lahikainen (1970) also found very low concentrations in middle ear secretion in 'catarrhal otitis' which he assumed to be caused by poorer capillary permeability of the middle ear mucosa due to the mild inflammatory condition. Ingvarsson et al. (1980) studied the concentration of penicillin V in middle ear exudate during the course of a 10-day treatment of AOM. The initially high middle ear exudate concentration fell to a significantly lower level even after 2-3 days' treatment. The lower concentration persisted during the rest of the treatment period. These results agree with the observations made by Lahikainen (1970). One might therefore question whether the penicillin treatment of 10 days in AOM can be shortened without impairing the results of healing or increasing the risk of complications. It was therefore decided to compare the effect of treatment with penicillin V for 5 and 10 days respectively, in children with AOM and, secondly, to find out whether a further increase in the penicillin dose would have a beneficial effect.

Table I. *Children with AOM arranged according to age, period, dose^a and duration of treatment*

Age (years)	Period I		Period II		Total
	2N×5	N×10	N×5	N×10	
0.5-1	19	25	9	18	71
2-4	39	36	36	35	146
5-7	24	20	21	15	80
Total	82	81	66	68	297

^a Normal dose (N): 25 mg/kg body weight twice a day.

MATERIAL AND METHODS

The clinical material consisted of 297 children, aged 6 months to 7 years, with acute purulent otitis media (AOM). All the cases were diagnosed and treated at the ENT Department, General Hospital, Malmö, Sweden. The criteria to be met for a clinical diagnosis were: a reddened and bulging eardrum with otoscopic signs of purulent otitis or with spontaneous perforation. The patients had not received antimicrobial agents because of otitis or other infections within the last 30 days before the study.

The investigation took place from October to December 1976 (period I) and from February to April 1977 (period II). The children were randomly divided into two groups during each period of the investigation. The potassium salt of penicillin V (Calciopen®, AB LEO, Helsingborg, Sweden) was given in a dose of either 25 or 50 mg/kg body weight twice a day. Table I shows the distribution of the patients according to age, period, daily dose of penicillin and duration of treatment. Of the 297 children, 217 (73%) were below 5 years of age. Altogether 148 children were treated with penicillin for 5 days, and 149 for 10 days. In addition, all the children received decongestants and analgetics when necessary. Nasopharyngeal material for bacterial culture was collected at the time of diagnosis.

The children were re-examined 10-12 days (control 1) and 28-30 days (control 2) after the

first consultation. All the examinations were done by two experienced otologists. The purpose of the first control after 10-12 days was to check whether the middle ear infection was abating although there were no claims for healing at that time. A new specimen for bacterial culture was taken from the nasopharynx. Furthermore, the parents were asked whether there had been any practical problems or side effects in association with the penicillin treatment. At control 2, healing was assessed. The children were regarded as having recovered if they had normal eardrums with normal mobility tested with a pneumatic otoscope and, in cases that could be investigated, normal hearing. Children were regarded as not healed if the eardrums showed serous otitis media (SOM) or if they had had a relapse (a new attack of otitis after completed antibiotic therapy) or therapeutic failure (insufficient effect of therapy or a new attack of otitis during antibiotic therapy). All the children were followed up for at least 6 months and any signs of otitis were registered.

RESULTS

The results of treatment are given in Table II. The frequency of healing among the children in the four groups varied between 74 and 80% (overall mean 78%). There was no difference ($p>0.2$) between the different groups referable to the daily dose or duration of treatment with penicillin. Healing was totally somewhat less good in the children below 2 years of age ($0.01<p<0.02$).

Among the 297 children, 66 (22%) did not meet the criteria for healing after 1 month (Table III), most often (42 cases) because of persistent SOM. A relapse was noted in 18 cases and therapeutic failure in 6. The four groups did not differ as regards persisting SOM, relapse, or therapeutic failure ($p>0.2$).

The medication caused no major problems in 287 (97%) of the children. Temporary side effects, e.g. nausea, diarrhea or refusal to take medicine, were reported on some occasion by

Table II. *Healing rate in relation to dose and duration of treatment in different ages judged at control 2*

Age (years)	Period I						Period II						Total		
	2N×5			N×10			N×5			N×10					
	T	H	%	T	H	%	T	H	%	T	H	%	T	H	%
0.5-1	19	14	74	25	15	60	9	7	78	18	14	78	71	50	70
2-4	39	26	67	36	30	83	36	28	78	35	26	74	146	110	75
5-7	24	24	100	20	15	75	21	18	86	15	14	93	80	71	89
Total	82	64	78	81	60	74	66	53	80	68	54	79	297	231	78

T = Total no. of children.

H = Total no. of children healed by control 2.

9 of these children, who nevertheless continued to take their medicine. Of the remaining 10 children, treatment was stopped too soon in 5 cases. In 2 cases because of refusal to take medicine, in 2 because of diarrhea and in 1 because of vomiting. This implied that the treatment periods were shortened by 1 to 3 days. However, this was considered negligible, for which reason these children were included in the investigation. In the last 5 cases the penicillin course could be continued after replacing the penicillin by another brand (Kåvepenin®, Astra Läkemedel AB, Södertälje, Sweden) with a different flavour but equal in dose.

Table IV shows the results of the nasopharyngeal cultures. Initially, pathogenic bacteria were found in about 75% of the cases. Continued nasopharyngeal growth of pathogenic bacteria was still seen in about 50% of the children after the end of treatment (control 1).

There were no inter-group differences referable to the dose or duration of treatment with penicillin.

New attacks of otitis (recurrences) within 6 months after control 2 are given in Table V. About 30% of the children treated during period I had a recurrence. The corresponding figure for period II was about 23%. In all the four groups recurrences were more common (39%) among the children below 2 years of age than in the older ones (23%). Among the children considered healed at control 2, 23% had a recurrence within the following 6 months compared with 41% of the children who were not healed by control 2.

DISCUSSION

Acute otitis media is a bacterial infection and is regarded as a complication of an upper respiratory tract infection. In Sweden, penicillin

Table III. *Cases not healed in relation to dose and duration of treatment at control 2*

Treatment	Cause of absence of healing			Total (%)
	SOM	Relapse	Therapeutic failure	
2N×5	10	6	2	18 (22)
N×10	16	4	1	21 (26)
N×5	8	4	1	13 (20)
N×10	8	4	2	14 (21)
Total	42 (64%)	18 (27%)	6 (9%)	66 (22)

Table IV. Occurrence (%) of pathogenic bacteria^a in nasopharynx before and after treatment

Treatment	Before treatment	After treatment (control 1)
2N×5	74	49
N×10	78	55
N×5	77	47
N×10	78	56

^a Pathogenic bacteria: *D. Pneumoniae*, *H. influenzae*, Haemolytic streptococci, *B. catarrhalis*.

V is still successfully used as the first drug of choice in the treatment of AOM. Studies on the concentration of penicillin in middle ear exudate have shown that a single dose of 25 mg/kg body weight has a satisfactory antibacterial effect in most cases of AOM, even those caused by *H. influenzae* (Kamme, 1969; Kamme et al., 1969). This dose, given twice a day (total daily dose = 50 mg/kg body weight) for 10 days, is just as effective as when the daily dose is divided into three doses (Lundgren, 1972; Rundcrantz & Sundför, 1974; Lorentzen & Haugsten, 1977). However, according to Ingvarsson et al. (1980), treatment for such a long time as 10 days might be questioned.

The present investigations were carried out during two different periods in order to assess the possible effect of the size of the penicillin dose as well as the duration of treatment on the results. The frequency of healing in the different groups varied only between 74% and

80%. Children treated for 5 days did not differ from those treated for 10 days. The increase in the single dose to 50 mg/kg body weight in one of the 5-day groups did not lead to improved healing.

The frequency of persisting SOM, relapse and therapeutic failure did not vary between the four groups. It was especially interesting to note the frequency of relapses in the 5-day groups. Earlier investigations (Lundgren, 1972) have shown that relapses caused by *D. pneumoniae* are common after a 10-day penicillin cure, presumably because of persisting pneumococcal growth in the nasopharynx. Relapses might therefore be expected to increase if treatment is shortened. However, no such increase occurred. Neither was the shorter treatment period followed by a higher incidence of recurrences within the following 6 months. The children in the first period of investigation had recurrences somewhat more often than the children in the second. This might be explained by the fact that the first observation period after diagnosis fell within the winter and early spring, when the frequency of upper respiratory tract infections was higher among children than during late spring and summer (the second observation period) according to statistical information about acute consultations at the ENT department, General Hospital, Malmö. Recurrences were most common among children below 2 years of age.

The growth of pathogenic nasopharyngeal bacteria was only slightly influenced by the penicillin therapy. This applies to most strains of *H. influenzae* as well as to *D. pneumoniae* and *B. catarrhalis*, which accords with earlier reports by Kamme et al. (1970) and Branefors-Helander et al. (1972). Judging from the present investigation, this growth does not vary with the length of treatment.

The results of the present study showed that shortening of the period of treatment from 10 to 5 days in AOM and retaining the same daily dose of penicillin V does not impair the results or increase the number of such complications

Table V. New attack of otitis within 6 months

Treatment	No. of children	New attack of otitis within 6 months	
		No.	%
2N×5	82	24	29
N×10	81	24	30
N×5	66	16	24
N×10	68	15	22
Total	297	79	27

as SOM, relapses or therapeutic failure. Neither does such shorter treatment imply an increasing risk of recurrent otitis. In view of the quantitative importance of this disease in childhood, shortening of the treatment would be advantageous. It would thus reduce the total consumption of antibiotics in children and thereby the risk of resistance developing among existing sensitive bacterial strains. The total time of exposure to penicillin would diminish, which possibly might reduce the risks of allergic reactions. The practical and financial consequences of such a shortening of the treatment would furthermore be of great importance to the single individual as well as to the entire community.

ZUSAMMENFASSUNG

297 Kinder im Alter von 6 Monaten bis 7 Jahren mit akuter Otitis Media (AOM) wurden mit Penicillin V behandelt. 148 Kinder erhielten 25 oder 50 mg pro kg Körpergewicht zweimal täglich während 5 Tage und 149 Kinder 25 mg pro kg Körpergewicht zweimal täglich während 10 Tage. In der Ausheilungsfrequenz wurden zwischen der 5- und der 10-Tage-Gruppe keine Unterschiede gefunden. Die größere Penicillindosis, die der Hälfte der 5-Tage-Gruppe gegeben worden war, führte nicht zu verbesserter Ausheilung. Behandlung mit Penicillin während 5 Tagen anstatt von 10 Tagen bedeutete keine zunehmende Gefahr für Komplikationen wie seröse Otitis Media (SOM), Rezidive oder therapeutische Mißerfolge. Darüber hinaus wurde auch die Gefahr einer Wiedererkrankung in Otitis nicht erhöht. Die Untersuchung ergab, daß die Behandlung von akuter Otitis mit Penicillin während 10 Tage, die in Schweden üblich ist, unter Beibehaltung von befriedigender Ausheilung und ohne Gefahr einer Erhöhung der Anzahl von Komplikationen auf 5 Tage reduziert werden kann.

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Leif Ingvarsson
Dept of Otolaryngology
University of Lund
Malmö General Hospital
S-21401 Malmö
Sweden

